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THE INTENSIVE CARE UNIT MANUAL

second edition

PAUL N. LANKEN
SCOTT MANAKER
BENJAMIN A. KOHL
C. WILLIAM HANSON, III

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The Intensive Care Unit Manual

PAUL N. LANKEN, MD
Professor of Medicine and Medical Ethics and Health Policy
Hospital of the University of Pennsylvania
Pulmonary, Allergy, and Critical Care Division
Department of Medicine
Associate Dean for Professionalism and Humanism
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

SCOTT MANAKER, MD, PhD
Associate Professor of Medicine and Pharmacology
Pulmonary, Allergy, and Critical Care Division
Perelman School of Medicine at the University of Pennsylvania
Vice Chair
Regulatory Affairs, Department of Medicine
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

BENJAMIN A. KOHL, MD, FCCM
Assistant Professor of Anesthesiology and Critical Care, and Internal Medicine
Chief, Division of Critical Care
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

C. WILLIAM HANSON III, MD
Professor of Anesthesia and Critical Care, Surgery, and Medicine
Perelman School of Medicine at the University of Pennsylvania
Former Medical Director
Surgical Intensive Care Unit
Chief Medical Information Officer and Vice President, Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

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To our teachers, colleagues, and students
Most importantly, to our families

Benjamin S. Abella, MD, MPhil
Clinical Research Director, Center for Resuscitation Science and Department of Emergency Medicine, University of Pennsylvania, Philadelphia, PA

Faten N. Aberra, MD, MSCE
Assistant Professor of Medicine, Division of Gastroenterology, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Gbemisola A. Adeseun, MD
Assistant Professor of Clinical Medicine, Keck School of Medicine, Division of Nephrology, University of Southern California, Los Angeles, CA

Nuzhat A. Ahmad, MD
Associate Professor of Medicine, Perelman School of Medicine, Associate Director, Endoscopic Services, Division of Gastroenterology, Hospital of the University of Pennsylvania, Philadelphia, PA

Steven R. Allen, MD
Assistant Professor of Surgery, Division of Traumatology, Surgical Critical Care, and Emergency Surgery, Department of Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

Zarina S. Ali, MD
Resident, Department of Neurosurgery, Hospital of the University of Pennsylvania, Philadelphia, PA

Pavan Atluri, MD
Assistant Professor of Surgery, Division of Cardiovascular Surgery, Department of Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Amanda M. Ball, PharmD, BCPS
Medical Intensive Care Unit Clinical Pharmacist, Wake Forest Baptist Medical Center, Winston-Salem, NC

Ramani Balu, MD, PhD
Fellow, Stroke and Neurocritical Care Division, Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA

Audreesh Banerjee, MD
Department of Medicine, Pulmonary, Allergy, and Critical Care Division, Hospital of the University of Pennsylvania, Philadelphia, PA

Danielle A. Becker, MD
Clinical Neurophysiology Fellow, Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA

Cassandra J. Bellamy, PharmD, BCPS
Clinical Pharmacy Specialist, Medical Intensive Care Unit, Hospital of the University of Pennsylvania, Philadelphia, PA

Jeffrey S. Berns, MD
Professor of Medicine and Pediatrics, Renal, Electrolyte, and Hypertension Division, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Shawn J. Bird, MD
Professor of Neurology, Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Marcelo Blaya, MD
Hematologist/Oncologist, Gurtler, Brinz, Burroff APMC, East Jefferson General Hospital, Metairie, LA

Melissa B. Bleicher, MD
Assistant Professor, Renal Electrolyte and Hypertension Division, Department of Medicine, University of Pennsylvania, Philadelphia, PA

Nina M. Bowens, MD
Resident, Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA

Jason C. Brainard, MD
Assistant Professor, Department of Anesthesiology, University of Colorado School of Medicine, Aurora, CO

Benjamin Braslow, MD, FACS
Associate Professor of Clinical Surgery, Division of Traumatology, Surgical Critical Care, and Emergency Surgery, Section Chief, Emergency Surgery Service, Department of Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

David Callans, MD
Associate Director of Electrophysiology, Hospital of the University of Pennsylvania, Philadelphia, PA

Megan E. Carr-Lettieri, MSN, ACNP-BC, CCRN
Nurse Practitioner, Medical Critical Care and Procedure and Rapid Response Team, Department of Clinical Staff Practitioners, Hospital of the University of Pennsylvania, Adjunct Clinical Instructor, University of Pennsylvania School of Nursing, Philadelphia, PA

Maurizio Cereda, MD
Assistant Professor, Department of Anesthesiology and Critical Care, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Pia Chatterjee, MD
Clinical Assistant Professor, Department of Emergency Medicine, New York University Bellevue Hospital Center, New York, NY

H. Isaac Chen, MD
Resident, Department of Neurosurgery, Hospital of the University of Pennsylvania, Philadelphia, PA

Debbie L. Cohen, MD
Associate Professor of Medicine, Director of Clinical Hypertension Programs, Co-Director of Pennsylvania Neuroendocrine Tumor Program, Department of Medicine, Renal Division, University of Pennsylvania, Philadelphia, PA

Jeffrey E. Cohen, MD
Resident in General Surgery, Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA

Gerald J. Criner, MD
Florence P. Bernheimer Distinguished Service Chair, Professor of Medicine, Department of Medicine, Chief, Section of Pulmonary and Critical Care Medicine, Director, Medical Intensive Care Unit and Ventilator Rehabilitation Unit, Temple University Hospital, Philadelphia, PA

Joel Dietz, MD
Clinical Associate Professor of Medicine, Department of Medicine, Division of Pulmonary Diseases and Critical Care, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Horace M. DeLisser, MD
Associate Professor of Medicine, Pulmonary, Allergy, and Critical Care Division, Department of Medicine at the Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Clifford S. Deutschman, MD, MS, FCCM
Professor of Anesthesiology and Critical Care, Director, Sepsis Research Program, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
President, Society of Critical Care Medicine, 2012

Joshua Diamond, MD, MSCE
Instructor, Pulmonary, Allergy, and Critical Care Division, University of Pennsylvania, Philadelphia, PA

Christopher T. Dibble, MD, MS
Former Fellow, Pulmonary, Allergy, and Critical Care Division, Hospital of the University of Pennsylvania, Philadelphia, PA

Jennifer M. Dolan, MS, RD, LDN, CNSC
Advanced Clinical Dietitian Specialist, Clinical Nutrition Support Service, Hospital of the University of Pennsylvania, Philadelphia, PA

Courtney L. Dostal, DO
Temple University Hospital, Philadelphia, PA

E. Wesley Ely, MD
Professor of Medicine, Department of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN

Douglas O. Faigel, MD, FACG, FASGE, AGAF
Professor of Medicine, Department of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, AZ

Victor A. Ferrari, MD
Professor of Medicine and Radiology, Department of Cardiovascular Medicine Cardiovascular Institute, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Barry Fields, MD
Fellow, Division of Sleep Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA

Neil Fishman, MD
Associate Professor of Medicine, Hospital of the University of Pennsylvania, Division of Infectious Diseases, Perelman School of Medicine at the University of Pennsylvania, Associate Chief Medical Officer, University of Pennsylvania Health System, Philadelphia, PA

Ian Frank, MD
Professor of Medicine, Division of Infectious Diseases, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Michael J. Frazer, BS, RRT, CPFT
Supervisor, Research Coordinator, Department of Respiratory Care, Hospital of the University of Pennsylvania, Philadelphia, PA

Andrew Freese, MD, PhD
Staff Neurosurgeon and Neurosurgical Medical Director, Brandywine Hospital, Coatesville, PA

David A. Fried, MD
Clinical Assistant Professor of Medicine, Department of Biomedicine, Brown University, Providence, RI

Barry D. Fuchs, MD, MS
Associate Professor of Medicine and Medical Director, Medical Intensive Care Unit and Respiratory Care, Hospital of the University of Pennsylvania, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Steven A. Fuhrman, MD
Medical Director, Sentara eICU, Sentara Healthcare, Norfolk, VA

Lee Gazourian, MD
Instructor of Medicine, Harvard Medical School, Department of Medicine, Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA

Joel D. Glickman, MD
Associate Professor of Clinical Medicine, Renal-Electrolyte and Hypertension Division, Hospital of the University of Pennsylvania, Philadelphia, PA

Stephen J. Gluckman, MD
Professor of Medicine, Clinical Director, Division of Infectious Diseases, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Andrew N. Goldberg, MD
Professor, Director, Division of Rhinology and Sinus Surgery, Department of Otolaryngology–Head and Neck Surgery and Neurological Surgery, University of California, San Francisco, San Francisco, CA

Lee R. Goldberg, MD, MSCE, FACS
Medical Director, Heart Failure and Cardiac Transplant Program, Cardiovasular Division, University of Pennsylvania, Philadelphia, PA

Stanley Goldfarb, MD, FACP, FASN, FCPP
Professor of Medicine, Associate Dean for Curriculum, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Diane Goodman, MD
Department of Neurology, Division of Stroke and Neurocritical Care, Hospital of the University of Pennsylvania, Philadelphia, PA

Jonathan E. Gottlieb, MD
Senior Vice President and Chief Medical Officer, University of Maryland Medical Center, Clinical Professor of Medicine, University of Maryland School of Medicine, Baltimore, MD

Vicente H. Gracias, MD
Professor of Surgery, Division of Acute Care Surgery, Department of Surgery, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ

Michael A. Grippi, MD
Vice Chairman, Department of Medicine, Pulmonary, Allergy, and Critical Care Division, Perelman School of Medicine at the University of Pennsylvania, Chief Medical Officer, GSPP Specialty Hospital, Philadelphia, PA

Indira Gurubhagavatula, MD, MPH
Assistant Professor of Medicine, Division of Sleep Medicine, Perelman School of Medicine at the University of Pennsylvania, Director, Sleep Disorders Clinic, Philadelphia VA Medical Center, Philadelphia, PA

Andrew R. Haas, MD, PhD
Assistant Professor of Medicine, Director, Clinical Operations, Section of Interventional Pulmonology and Thoracic Oncology, Pulmonary, Allergy, and Critical Care Division, Hospital of the University of Pennsylvania, Philadelphia, PA

Keith Hamilton, MD
Associate Director, Healthcare Epidemiology, Infection Prevention and Control, Hospital of the University of Pennsylvania, Associate Co-Director of Internal Medicine Clerkship and Instructor, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

C. William Hansen III, MD
Professor of Anesthesia and Critical Care, Surgery, and Internal Medicine, Perelman School of Medicine at the University of Pennsylvania, Chief Medical Information Officer and Vice President, Hospital of the University of Pennsylvania, Philadelphia, PA

Robin Hermann, MSN, RN, CCRP
Clinical Nurse IV, Medical Intensive Care Unit, Hospital of the University of Pennsylvania, Philadelphia, PA

John R. Hess, MD, MPH, FACP, FAAAS
Professor of Pathology and Medicine, University of Maryland School of Medicine, Baltimore, MD

Kolin Hoff, MD
Assistant Professor of Clinical Medicine, Division of Endocrinology, Diabetes, and Metabolism, Hospital of the University of Pennsylvania, Philadelphia, PA

Linda Hoke, MD
Clinical Nurse Specialist, Cardiac Intermediate Care Unit, Hospital of the University of Pennsylvania, Philadelphia, PA

Daniel N. Holena, MD, FACS
Assistant Professor of Surgery, Division of Traumatology, Surgical Critical Care, and Emergency Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA

Kristin Hudock, MD
Instructor, Pulmonary, Allergy, and Critical Care Division, University of Pennsylvania, Philadelphia, PA

Warren Isakow, MD
Assistant Professor of Medicine, Pulmonary, and Critical Care Medicine, Washington University School of Medicine, St. Louis, MO

David R. Janz, MD
Clinical Fellow, Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, TN

Arminder Jassar, MBBS
Chief Resident, Department of Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Kevin D. Judy, MD
Professor of Neurosurgery, Thomas Jefferson University, Jefferson Medical College, Department of Neurosurgery, Philadelphia, PA

Marc J. Kahn, MD, MBA
Peterman-Prosser Professor, Senior Associate Dean, Department of Medicine, Section of Hematology/Medical Oncology, Tulane University School of Medicine, New Orleans, LA

Mitul B. Kadakia, MD
Division of Cardiovascular Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Suraj Kapa, MD
Fellow, Cardiac Electrophysiology, Division of Electrophysiology, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA

Scott E. Kasner, MD
Professor of Neurology, Perelman School of Medicine at the University of Pennsylvania, Director, Comprehensive Stoke Center, University of Pennsylvania Health System, Philadelphia, PA

Joshua B. Kayser, MD, MPH
Assistant Professor of Clinical Medicine, Pulmonary, Allergy, and Critical Care Division, Perelman School of Medicine at the University of Pennsylvania, Director, Medical Intensive Care Unit, Philadelphia VA Medical Center, Philadelphia, PA

Scott A. Keeney, DO
Fellow, Department of Trauma, Surgical Critical Care, and Emergency Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA

Patrick K. Kim, MD
Assistant Professor of Surgery, Division of Traumatology, Surgical Critical Care, and Emergency Surgery, Department of Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Stephen Kim, MD
Resident, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA

Rhonda S. King, MD
Washington Hospital Center, Washington, DC

Melissa L. Kirkwood, MD
Assistant Professor of Surgery, Division of Vascular and Endovascular Surgery, UT Southwestern Medical Center, Dallas, TX

Sidney M. Kobrin, MD, MBBS
Associate Professor of Medicine, Director, Inpatient and Radnor Dialysis, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Benjamin A. Kohl, MD, FCCM
Assistant Professor of Anesthesiology and Critical Care, and Internal Medicine, Chief, Division of Critical Care, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Daniel M. Kolansky, MD
Associate Professor of Medicine, Division of Cardiovascular Medicine, Perelman School of Medicine at the University of Pennsylvania, Director, Cardiac Care Unit, Hospital of the University of Pennsylvania, Philadelphia, PA

Mark J. Kotapka, MD
Chairman, Division of Neurosurgery, Department of Surgery, Einstein Health Care Network, Philadelphia, PA

Stephen J. Kovach, MD
Assistant Professor of Surgery, Division of Plastic Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Maryl Kreider, MD, MSCE
Assistant Professor of Medicine, Co-Director of Interstitial Lung Disease Program, Associate Program Director, Education and Fellowship Program for Pulmonary Medicine, Medical Director, Pulmonary Diagnostics Laboratory, Hospital of the University of Pennsylvania, Philadelphia, PA

Karen L. Krok, MD
Assistant Professor of Medicine, Division of Gastroenterology, Department of Medicine, University of Pennsylvania, Philadelphia, PA

Rebecca Kruse-Jarres, MD, MPH
Assistant Professor of Medicine, Tulane University, New Orleans, LA

John C. Kucharczuk, MD
Associate Professor, Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA

Daniel J. Landsburg, MD
Chief, Division of Thoracic Surgery, and Fellow, Division of Hematology/Oncology, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Meghan B. Lane-Fall, MD, MSHP
Attending Physician, Anesthesiology, Department of Anesthesiology and Critical Care, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Paul N. Lanken
Professor of Medicine and Medical Ethics and Health Policy, Hospital of the University of Pennsylvania, Pulmonary, Allergy, and Critical Care Division, Department of Medicine, Associate Dean for Professionalism and Humanism, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Marion Leary, RN, BSN
Assistant Director of Clinical Research, Center for Resuscitation Science, Department of Emergency Medicine, University of Pennsylvania, Philadelphia, PA

David N. Levine, MD
Professor of Neurology, New York University School of Medicine, New York, NY

Joshua M. Levine, MD
Assistant Professor, Departments of Neurology, Neurosurgery, and Anesthesiology and Critical Care, Co-Director, Neurocritical Care Program, Hospital of the University of Pennsylvania, Philadelphia, PA

Lisa D. Levine, MD
Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Gary R. Lichtenstein, MD
Professor of Medicine, Division of Gastroenterology, Perelman School of Medicine at the University of Pennsylvania, Director, Center for Inflammatory Bowel Disease, Hospital of the University of Pennsylvania, Philadelphia, PA

Craig M. Lilly, MD
Professor of Medicine, Anesthesiology, and Surgery, Department of Medicine, University of Massachusetts Medical School, Worcester, MA

Scott M. Lilly, MD
Assistant Professor, Interventional Cardiology, The Richard M. Ross Heart Hospital, The Ohio State University Medical Center, Columbus, Ohio.

Alison W. Loren, MD, MS
Assistant Professor of Medicine, Fellowship Program Director, Division of Hematology/Oncology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

David W. Low, MD
Professor of Surgery, Division of Plastic Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Cheryl Maguire
Nurse Manager, Medical Intensive Care Unit, Hospital of the University of Pennsylvania, Philadelphia, PA

Junsuke Maki, MD
Fellow, Division of Gastroenterology, Hospital of the University of Pennsylvania, Philadelphia, PA

Kelly M. Malloy, MD, FACS
Assistant Professor, Department of Otolaryngology—Head and Neck Surgery, University of Michigan Health System, Ann Arbor, MI

Daniel Malone, PT, PhD, CCS
Assistant Professor, Physical Medicine and Rehabilitation, Physical Therapy Program, University of Colorado Denver, Denver, CO

Stephen A. Malosky, MD
Interventional Cardiologist, Aultman Hospital, Faculty, Aultman Hospital Cardiology Fellowship Program, Canton Ohio

Scott Manaker, MD, PhD
Associate Professor of Medicine and Pharmacology, Pulmonary, Allergy, and Critical Care Division, Perelman School of Medicine at the University of Pennsylvania, Vice Chair, Regulatory Affairs, Department of Medicine, Hospital of the University of Pennsylvania, University of Pennsylvania Health System, Philadelphia, PA

Andrew Mannes, MD
Chief, Department of Perioperative Medicine, National Institutes of Health, Bethesda, MD

Francis E. Marchlinski, MD
Professor of Medicine, Perelman School of Medicine at the University of Pennsylvania, Director, Cardiac Electrophysiology, Hospital of the University of Pennsylvania, Philadelphia, PA

Paul Marcotte, MD
Associate Professor of Neurosurgery, Department of Neurosurgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Neil M. Masangkay, MD
Instructor, Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Kara B. Mascitti, MD, MSCE
Director, Healthcare Epidemiology and Infection Prevention, St. Luke's University Health Network, Bethlehem, PA

Fenton McCarthy, MD
Resident, Division of Cardiovascular Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA

Michael L. McGarvey, MD
Associate Professor of Neurology, Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA

C. Crawford Mechem, MD
Associate Professor, Department of Emergency Medicine, Hospital of the University of Pennsylvania, EMS Medical Director, Philadelphia Fire Department, Philadelphia, PA

Samir Mehta, MD
Chief, Orthopaedic Trauma and Fracture Service, Department of Orthopaedic Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA

Paul Menard-Katcher, MD
Assistant Professor, Division of Gastroenterology and Hepatology, University of Colorado Denver, Aurora, CO

Nuala J. Meyer, MD, MS
Assistant Professor, Department of Medicine, Pulmonary, Allergy, and Critical Care Division, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Mark E. Mikkelsen, MD, MSCE
Assistant Professor of Medicine, Pulmonary, Allergy, and Critical Care Division, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Bonnie L. Milas, MD
Associate Professor of Clinical Anesthesiology and Critical Care, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Natasha Mirza, MD, FACS
Professor, Department of Otolaryngology, Head and Neck Surgery, Chief, Otolaryngology, VA Medical Center, Director, Pennsylvania Voice and Swallowing Center, Hospital of the University of Pennsylvania, Philadelphia, PA

Edmund K. Moon, MD
Section of Interventional Pulmonary and Thoracic Oncology, Pulmonary, Allergy, and Critical Care Division, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Jennifer S. Myers, MD
Associate Professor of Clinical Medicine, Department of Medicine, Patient Safety Officer, Hospital of the University of Pennsylvania, Director of Quality and Safety Education, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Giora Netzer, MD, MSCE
Assistant Professor of Medicine and Epidemiology, Director of Clinical Research, Division of Pulmonary and Critical Care Medicine, Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD

Christopher Nold, MD
Department of Obstetrics and Gynecology, Hospital of the University of Pennsylvania, Philadelphia, PA

David A. Oxman
Assistant Professor of Medicine, Division of Pulmonary and Critical Care, Jefferson Medical College, Philadelphia, PA

Alix O. Paget-Brown, MD
Assistant Professor of Pediatrics, Clinical Director, Neonatal Emergency Transport System, Department of Pediatrics, University of Virginia, Charlottesville, VA

Harold I. Palevsky, MD
Professor of Medicine, Perelman School of Medicine at the University of Pennsylvania, Chief, Pulmonary, Allergy and Critical Care, Director, Pulmonary Vascular Disease Program, Pennsylvania Presbyterian Medical Center, Philadelphia, PA

Reynold A. Panettieri Jr., MD
Robert L. Mayock and David A. Cooper Professor of Medicine, Pulmonary, Allergy and Critical Care Division, Director, Airways Biology Initiative, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Samuel Parry, MD
Director, Maternal Fetal Medicine Division, Member, Center for Research on Reproduction and Women's Health, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Jose L. Pascual, MD, PhD, FRCS(C), FRCP(C), FACS
Assistant Professor of Surgery, Department of Surgery, Division of Trauma, Emergency Surgery and Critical Care, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Nirav P. Patel, MD, MPH†
Adjunct Assistant Professor of Medicine, Division of Sleep Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, Attending Physician, The Reading Hospital and Medical Center and St. Joseph's Medical Center, Reading, PA

Taine T.V. Pechet, MD, FACS
Associate Professor of Clinical Surgery, Perelman School of Medicine at the University of Pennsylvania, Vice Chief of Surgery, Pennsylvania Presbyterian Medical Center, Division of Thoracic Surgery, University of Pennsylvania, Philadelphia, PA

Jeanmarie Perrone, MD, FACMT
Director, Division of Medical Toxicology, Associate Professor, Department of Emergency Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Matthew F. Phillips, MD
Southcoast Neurosurgery, North Dartmouth, MA

Travis M. Polk, MD, FACS
Instructor in Surgery, Division of Traumatology, Surgical Critical Care, and Emergency Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

†Deceased.

Ave Maria Preston, MSN, RN, CWOCN
Clinical Nurse Specialist, Department of Surgical Nursing, Hospital of the University of Pennsylvania, Philadelphia, PA

Amy J. Reed, MD, PhD
Instructor of Anesthesia, Harvard Medical School, Department of Anesthesia, Critical Care, and Pain Medicine, Beth Israel Deaconess Medical Center, Boston, MA

Eugene F. Reilly, MD, FACS
Clinical Assistant Professor of Surgery, Trauma Surgeon, University of Pennsylvania, Philadelphia PA, The Reading Hospital and Medical Center, West Reading, PA

James B. Reilly, MD, MSHP, FACP
Chief, Division of Trauma and Surgical Critical Care, and Assistant Professor of Clinical Medicine, Department of Medicine, Division of Nephrology, Perelman School of Medicine at the University of Pennsylvania, Director of Residency Training, Pennsylvania Presbyterian Medical Center, Associate Residency Director, Internal Medicine Residency, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

John P. Reilly, MD
Fellow, Division of Pulmonary, Allergy, and Critical Care, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Patrick M. Reilly, MD, FACS
Professor of Surgery, Department of Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Michael Ries, MD, MBA (FCCM, FCCP, FACP)
Medical Director, Critical Care and eICU Advocate Healthcare, Associate Professor of Medicine, Department of Pulmonary and Critical Care Medicine, Rush University, Chicago, IL

Ilene M. Rosen, MD, MSCE
Director, Sleep Medicine Fellowship, Associate Program Director, Internal Medicine Residency, Divisions of Sleep Medicine and Pulmonary, Allergy, and Critical Care, Perleman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Misha Rosenbach, MD
Assistant Professor, Dermatology and Internal Medicine, Director, Dermatology Inpatient Consult Service, Departments of Dermatology and Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Michael R. Rudnick, MD, FACP, FASN
Associate Professor of Medicine, Perleman School of Medicine at the University of Pennsylvania, Chief, Nephrology Division, Pennsylvania Presbyterian Medical Center, Philadelphia, PA

Uzma Samadani, MD, PhD, FACS
Chief Neurosurgeon, New York Harbor Health Care System, Assistant Professor, Department of Neurosurgery, New York University, New York, NY

Babak Sarani, MD
Associate Professor of Surgery, George Washington University, Washington, DC

Aharon Sareli, MD
(Former) Assistant Professor of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Aditi Satti, MD
Assistant Professor of Medicine, Temple University Hospital, Philadelphia, PA

Richard J. Schwab, MD
Professor, Department of Medicine, Division of Sleep Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA

William Schweickert, MD
Assistant Professor of Medicine, Pulmonary, Allergy, and Critical Care Division, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Benjamin K. Scott, MD
Assistant Professor, Department of Anesthesiology, University of Colorado School of Medicine, Aurora, CO

Miriam Segal, MD
Attending Physician, Department of Physical Medicine and Rehabilitation, Moss Rehab at Elkins Park, Albert Einstein Medical Center, Elkins Park, PA

Bilal Shafi, MD
Fellow, Division of Cardiothoracic Surgery, University of Pennsylvania, Philadelphia, PA

Chirag V. Shah, MD, MSc
Medical Director, Intensive Care Unit, Morristown Medical Center, Atlantic Health System, Morristown, NJ

Siddharth P. Shah, MD
Assistant Professor of Clinical Medicine, Renal-Electrolyte and Hypertension Division, University of Pennsylvania, Philadelphia, PA

Michael G. Shashaty, MD, MSCE
Instructor of Medicine, Division of Pulmonary, Allergy, and Critical Care, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Adam M. Shiroff, MD, FACS
Trauma Program Director, Assistant Professor of Surgery, Division of Acute Care Surgery, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ

Don L. Siegel, MD, PhD
Professor and Director, Division of Transfusion Medicine and Therapeutic Pathology, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA

Una O'Doherty Siegel, MD, PhD
Associate Professor, Director of the Stem Cell Laboratory, Department of Pathology and Laboratory Medicine, Division of Transfusion Medicine and Therapeutic Pathology, University of Pennsylvania, Philadelphia, PA

Frank E. Silvestry, MD
Associate Professor of Medicine, Division of Cardiovascular Medicine, Department of Medicine, Perelman School of Medicine, at the University of Pennsylvania, Philadelphia, PA

Melissa A. Simonian, M.Ed, CCC-SLP
Director, Speech-Language Pathology, Braintree Rehabilitation Hospital, Braintree, MA

Carrie A. Sims, MD, MS, FACS
Assistant Professor in Surgery, Division of Traumatology and Surgical Critical Care, University of Pennsylvania, Philadelphia, PA

Michael W. Sims, MD, MSCE
Assistant Professor of Medicine, Division of Pulmonary, Allergy, and Critical Care, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Robert A. Sinkin, MD, MPH
Professor of Pediatrics, Division Head Neonatology, Medical Director, Neonatal Intensive Care Unit, Department of Pediatrics, University of Virginia, Charlottesville, VA

Michael J. Soisson, MS, MHA
(Former) Executive Director, Good Shepherd Pennsylvania Partners Specialty Hospital, Philadelphia, PA

Jeremy Souder, MD
Clinical Assistant Professor of Medicine, Division of General Internal Medicine, Department of Medicine, Patient Safety Officer, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Bernie Sunwoo, MB, BS
Assistant Professor, Department of Medicine, Division of Pulmonary, Allergy, and Critical Care, Division of Sleep Medicine, Perelman School of Medicine at the Hospital of the University of Pennsylvania, Philadelphia, PA

Gregory E. Supple, MD
Assistant Professor of Medicine, Cardiovascular Division/Electrophysiology, Hospital of the University of Pennsylvania, Philadellphia, PA

Patricia Takach, MD, FAAAAI
Assistant Professor, Section of Allergy and Immunology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Naasha Talati, MD, MSCR
Clinical Assistant Professor, Department of Medicine, Division of Infectious Diseases, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Nabil Tariq, MD
Minimally Invasive and Bariatric Surgery, DuPage Medical Group, Central DuPage Hospital, Winfield, IL

Erica R. Thaler, MD, FACS
Professor, Department of Otolaryngology, Head and Neck Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Arthur C. Theodore, MD
Associate Professor of Medicine, Pulmonary, Allergy and Critical Care Medicine, Boston University School of Medicine, Boston, MA

Mitchell D. Tobias, MD
Professor of Anesthesiology, Virginia Commonwealth University, Department of Anesthesia, INOVA Fairfax Hospital, Falls Church, VA

Raymond R. Townsend, MD
Professor of Medicine, Renal, Electrolyte, and Hypertension Division, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Jason B. Turowski, MD
Fellow, Pulmonary, Allergy, and Critical Care Division, Hospital of the University of Pennsylvania, Philadelphia, PA

Tanya J. Uritsky, PharmD, BCPS
Clinical Pharmacy Specialist, Pain Management and Palliative Care, Hospital of the University of Pennsylvania, Philadelphia, PA

Esther Vorovich, MD
Fellow, Department of Cardiovascular Medicine, University of Pennsylvania, Philadelphia, PA

Alisha N. Wade, MBBS (Hons), DPhil
Clinical Scientist, Division of Endocrinology and Metabolism, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, ZAF

Alexander W. Washington Jr., MD
Clinical Assistant Professor of Medicine, Department of Hematology and Medical Oncology, Tulane University School of Medicine, New Orleans, LA

Alan G. Wasserstein, MD
Associate Professor of Medicine, Renal, Electrolyte and Hypertension Division, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Gerald L. Weinhouse, MD
Assistant Professor of Medicine, Harvard Medical School, Department of Medicine, Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA

Marissa B. Wilck, MBChB, MS
Assistant Professor, Department of Medicine, Division of Infectious Diseases, Hospital of the University of Pennsylvania, Philadelphia, PA

Noel N. Williams, MD
Professor of Surgery, Director, Bariatric Surgery Program, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

F. Perry Wilson, MD
Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Kevin C. Wilson, MD
Assistant Professor of Medicine, Department of Medicine, Boston University School of Medicine, Boston, MA

Laura Wolfe, MD
Denver Digestive Health Specialists, Denver, CO

Edward Y. Woo, MD
Associate Professor, Department of Surgery, Perelman School of Medicine at the University of Pennsylvania, Vice-Chief and Program Director, Division of Vascular Surgery and Endovascular Therapy, Director, Vascular Laboratory, Hospital of the University of Pennsylvania, Philadelphia, PA

Eric L. Zager, MD
Professor, Department of Neurosurgery, Hospital of the University of Pennsylvania, Philadelphia, PA

Ting Zhou, MD
Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA

PREFACE TO FIRST EDITION

"Why does the world need another ICU textbook?" asked one prospective contributor shortly after this project began. It was not exactly what I had expected to hear at the time. It turned out, however, to be an excellent question, whose answer, like a landmark on the horizon, has guided this book along its journey to completion. The answer lies in my original vision for this book: to create a manual of critical care medicine that would be especially useful for housestaff in medical, cardiac, and surgical intensive care units (ICUs). As such, it would have to be *comprehensive, concise,* and *practical.*

The book needed to be *comprehensive* to help ICU housestaff perform many jobs successfully—no matter what kind of ICU they were in. If the book had a motto, it would be "It's all here!" The 98 chapters of *The Intensive Care Unit Manual* encompass the scope and complexity of critical care medicine that ICU housestaff encounter. Included are not only descriptions of common, important disorders that result in ICU admission, but also instructions about how to evaluate and manage problems that arise *after* ICU admission. The book covers the practices of many specialists, and its content reflects both the medical literature and literally hundreds of "author-years" of critical care experience.

The book had to be *concise* to make it readable for ICU housestaff who are often on-call. But making it concise mandated that contributors and editors drastically condense many chapters without disrespecting the importance of their topics. One contributor not so subtly commented to me that entire books had been written about his assigned topic—as he handed me his 8 pages of galley proofs.

If the book were not *practical,* it would have missed its mark entirely. For housestaff on call in ICUs, critical care medicine is first and foremost a practical endeavor. They need practical resources to help them deal with the practical problems that arise in the ICU setting.

Do not read *The Intensive Care Unit Manual* as if it were a novel. Instead, read the parts you need to take care of your patients. The first three sections of the book contain basic ICU principles and practices, and care of "generic" and "special" patients. Next come the *problem-based* chapters that focus on evaluation and management of problems arising *after* ICU admission. The final section contains a traditional menu of common *ICU admitting diagnoses* followed by chapters pertaining to *postoperative ICU care* after major surgery and trauma.

As you use this manual "in the trenches," you may discover important topics that were omitted or need more emphasis. How can this manual be more useful for you? We welcome your opinions and feedback, preferably by email (lanken@mail.med.upenn.edu).

This book is the product of many people. I greatly appreciate all their contributions and encouragement. I especially want to thank Richard Zorab, Editor-in-Chief, Medicine of W.B. Saunders Company. Not only did he share my vision for this book from its start but, more importantly, he also has been absolutely essential in the challenging process of transforming that vision into this final product.

Paul N. Lanken, MD

PREFACE TO SECOND EDITION

The aim of the second edition of *The Intensive Care Unit Manual* remains the same as the first edition: to provide a handbook for critical care clinicians, particularly residents and fellows, that is *comprehensive, concise,* and *practical*.

More than 10 years have passed since the first edition was published. We updated the content of the 91 chapters carried over from the first edition accordingly. We also broadened the book's scope by adding 21 new chapters that reflect advances in medical knowledge and patient care as well as today's reality in practicing critical care medicine (e.g., as a multi-disciplinary team in the context of culturally competent and family-centered care). Our total of 112 chapters benefited greatly by having "room to expand" online, including all of the updated annotated bibliographies for each chapter plus other important text, tables, and figures.

With these updated and new chapters, this manual now encompasses all six of the core clinical competencies that the Accreditation Council for Graduate Medical Education (ACGME) requires as outcomes for all US residency programs (see Common Program Requirements at www.acgme.org).

Sections 1 through 5 of the manual reflect the ACGME competencies of Patient Care and Medical Knowledge as well as some elements of Practice-based Learning and Improvement. New chapters in these sections include key clinical topics in the practice of contemporary critical care medicine: use of noninvasive ventilation, management of alcohol withdrawal syndrome, care of morbidly obese medical and surgical patients, diagnosis, prevention and management of delirium, therapeutic hypothermia after cardiac arrest, management of acute decompensation of patients with chronic heart failure, and alternative modes of ventilation.

Sections 6 and 7, new to this edition, contain the chapters that represent the ACGME core competencies of Professionalism, Interpersonal and Communication Skills, and Systems-based Practice. I invite the reader to flip through Chapters 102 to112 in Sections 6 and 7 (or their titles in the Table of Contents) to see their specific topics.

We welcome your email comments, especially how you think we can make this manual even more useful to you (paul.lanken@uphs.upenn.edu).

Needless to say, it's been extremely satisfying to me to see this book take shape as envisioned and become a reality for a second time. Like the first edition, it is the product of many people's efforts.

I would be seriously remiss if I didn't first thank my co-editors, Drs. Scott Manaker, Ben Kohl, and Bill Hanson, for their work, commitment, and enthusiasm.

Likewise, my sincere appreciation goes to our collaborators at Elsevier Inc. for their patience and encouragement and for sharing our commitment to creating a high-quality product. These include Bill Schmitt, Sharon Corell, Julia Rose Roberts, Heather Krehling, and Agnes Byrne.

Finally, I speak for all of the editors and publishers' representatives in thanking the authors of this edition's 112 chapters whose dedication and hard work helped make this manual possible. With their contributions, I'm confident that the manual will stay on target in meeting its original aim–to serve as a *comprehensive, concise* ,and *practical* handbook for clinicians in caring for their critically ill and injured patients.

Paul N. Lanken, MD

CHAPTER 1

Approach to Acute Respiratory Failure

Paul N. Lanken

Arguably, more than any other device, mechanical ventilators symbolize intensive care and intensive care units (ICUs). Ventilators provide the most basic form of life support to critically ill or injured patients. The nearly ubiquitous presence of mechanical ventilators in ICUs reflects how commonly patients in the ICU have acute respiratory failure. In caring for these patients, ICU clinicians must decide when to start, change, or stop assisted ventilation. Knowing the mechanism that caused a patient's acute respiratory failure helps in making these decisions and in determining what needs to improve so that the patient can breathe spontaneously again.

Despite having many causes, acute respiratory failure results from only a few basic pathophysiologic mechanisms. Thus, a mechanism-based approach to evaluation and management can be applied to a wide spectrum of patients with acute respiratory failure of different causes. Knowing the mechanism of respiratory failure involved in specific clinical disorders allows the ICU clinician to direct treatment effectively and efficiently.

Definitions

Acute respiratory failure is the final common pathway for diverse clinical disorders. *Acute* refers to an onset usually measured in terms of hours or days (i.e., less than 7 days) . *Respiratory failure* indicates a severe impairment of pulmonary gas exchange; it is categorized into two types. *Hypercapnic respiratory failure* occurs when a patient's $Paco_2$ rises to greater than normal—that is, greater than 45 mm Hg. *Hypoxemic respiratory failure* occurs when a patient's Pao_2 falls so low that it is life-threatening or has serious adverse physiologic effects. For example, in cases of acute hypoxemic respiratory failure, Pao_2 is often less than 55 mm Hg despite the administration of high, potentially toxic concentrations of oxygen. A Pao_2 of 55 mm Hg corresponds to a modestly reduced arterial hemoglobin saturation of about 88%. This is near the top of the steep part of the oxygen-hemoglobin (O_2-Hgb) dissociation curve, and further decrements result in steep, linear falls in arterial O_2 content (see Figures A1 and A2 in Appendix A for O_2-Hgb dissociation curves).

Four Components of the Respiratory System

The *respiratory system* can be regarded as having four functional and structural components: (1) the central nervous system (CNS) component (chemoreceptors, the controller [respiratory center in the medulla], and CNS efferents); (2) the chest bellows component (composed of the peripheral nervous system, respiratory muscles, and the chest wall and soft tissues surrounding the lung); (3) the airway component; and (4) the alveolar component. Together they form the *effector arm* of the respiratory system's feedback and control loop (Figure 1.1).

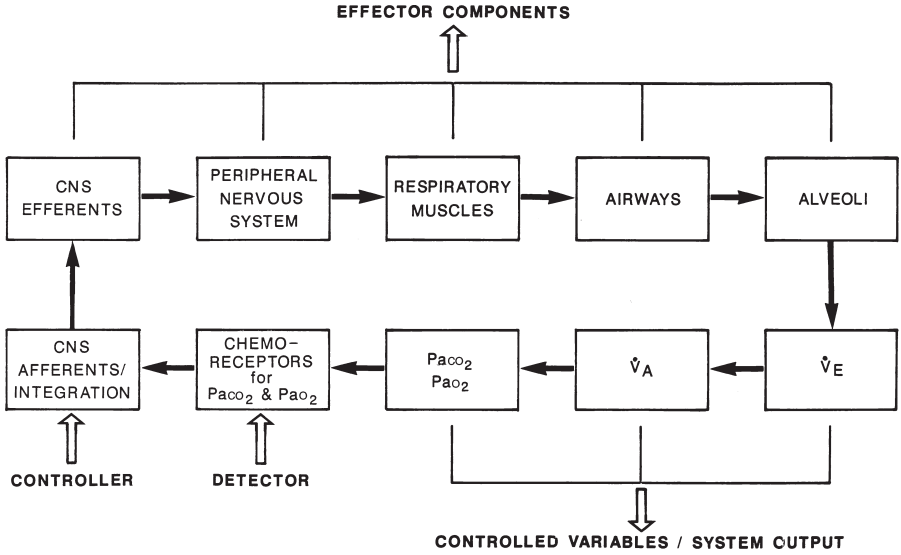


Figure 1.1 The feedback loop of the respiratory system. Its effector components consist of the central nervous system (CNS) drive to ventilate, neural connections to the respiratory muscles, the muscles themselves, conducting airways, and alveoli. The controlled variables (system output) consist of minute ventilation ($\dot{V}_E$), alveolar ventilation ($\dot{V}_A$), $Paco_2$, and Pao_2. Changes in Pao_2 and $Paco_2$ are detected by peripheral and central chemoreceptors (detector), which then send information to the CNS respiratory center (controller). The controller maintains homeostasis by increasing or decreasing activity of the effector components in response to abnormalities in Pao_2 or $Paco_2$. *(From Lanken PN: Respiratory failure. In Carlson RW, Geheb MA [eds]: Principles and Practice of Medical Intensive Care. Philadelphia: WB Saunders, 1993, pp 754-763.)*

When all four components function correctly, their sequential actions result in normal pulmonary gas exchange:

1. The CNS controller initiates respiratory drive by generating neural output. The rate and intensity of its output are determined by the feedback provided by peripheral chemoreceptors (monitoring Pao_2 and $Paco_2$) and central chemoreceptors (monitoring $Paco_2$ or its effects) and by input from other neural sources.
2. The neural impulses from the CNS controller traverse the spinal cord and the phrenic and other motor neurons and reach the diaphragm and other respiratory muscles.
3. In response, these muscles expand the chest cavity, displace adjacent abdominal contents, and produce negative (subatmospheric) pleural pressure within the thorax.
4. This negative pressure is transmitted to the alveoli, creating a gradient between the alveoli and atmospheric pressure at the mouth. In response, air flows through the conducting airways to the alveoli, leading to lung inflation.
5. Finally, alveolar O_2 passively diffuses across the alveolar-capillary membrane so that red blood cells become fully equilibrated with alveolar Po_2 as they pass through alveolar capillaries. The same process, but in the reverse direction, occurs for CO_2.

Respiratory Pump and Control of $Paco_2$

Under normal conditions, the feedback and control loop (see Figure 1.1) maintain the system's set point for $Paco_2$ at 40 mm Hg. Pathologic conditions, however, can move this set point up or down. Under such circumstances, the CNS controller tries to achieve the "proper" level of $Paco_2$ at this new set point by changing minute ventilation.

BOX 1.1 ■ Basic Physiologic Equations

Equation 1: $\dot{V}_E = V_T \times RR$

where $\dot{V}_E$ is the expired minute ventilation, V_T is the tidal volume, and RR is the respiratory rate

Equation 2: $PaCO_2 = K \times \dot{V}CO_2/\dot{V}_A$

where K is a constant (863 mm Hg), $\dot{V}co_2$ is CO_2 production per minute, and $\dot{V}_A$ is alveolar ventilation

Equation 3: $V_T = V_A + V_D$

where V_A is the part of the tidal volume that contributes to alveolar ventilation, and V_D is the dead space (i.e., that part of the tidal volume not contributing to gas exchange)

Equation 4: $\dot{V}_E = \dot{V}_A + \dot{V}_D$

where $\dot{V}_A$ is alveolar ventilation ($\dot{V}_A = V_A \times RR$), and $\dot{V}_D$ is dead space ventilation ($\dot{V}_D = V_D \times RR$)

Equation 5: $\dot{V}_D = V_D \times RR = V_D(\dot{V}_E/V_T) = (V_D/V_T) \times \dot{V}_E$

where $RR = \dot{V}_E/V_T$ by rearranging Equation 1, and V_D/V_T is the dead space to tidal volume ratio

Equation 6: $\dot{V}_E = \dot{V}_A + \dot{V}_D = \dot{V}_A + \dot{V}_E (V_D/V_T)$

where $\dot{V}_D$ in Equation 4 is replaced by $\dot{V}_E(V_D/V_T)$ as derived in Equation 5

Equation 7: $\dot{V}_E = \dot{V}_A/(1 - V_D/V_T)$

which is derived by solving Equation 6 for $\dot{V}_E$

Equation 8: $\dot{V}_A = \dot{V}_E \times (1 - V_D/V_T)$

which is derived by solving Equation 6 for $\dot{V}_A$

Equation 9: $Paco_2 = K \times \dot{V}co_2/[(1 - V_D/V_T) \times \dot{V}_E]$

after right-hand side of Equation 8 is substituted for $\dot{V}_A$ in Equation 2

Equation 10: $Paco_2 \times \dot{V}_E = K \times \dot{V}co_2/(1 - V_D/V_T)$

which is derived from Equation 9 by rearrangement of the term $\dot{V}_E$

Equation 11: $\dot{V}_E = K \times \dot{V}co_2/[Paco_2 \times (1 - V_D/V_T)]$

which solves Equation 10 for $\dot{V}_E$

Equation 12 (Alveolar Gas Equation): $P_{AO_2} = P_{IO_2} - P_{ACO_2}/R$

where P_{AO_2} is mean ideal alveolar P_{O_2}, P_{IO_2} is the inspired P_{O_2}, P_{ACO_2} is the alveolar P_{CO_2} estimated as equal to $Paco_2$, and R is the respiratory ratio, usually assumed to be 0.8 (except when $F_{IO_2} = 1.0$, R = 1); R is the non–steady-state equivalent of the steady-state respiratory quotient, RQ, which is defined as $\dot{V}co_2/\dot{V}o_2$

Because the actions of the respiratory system's first three components (CNS, chest bellows, and airway) determine a patient's minute ventilation, they have been called the *respiratory pump*. Minute ventilation can be increased or decreased by the respiratory pump by changing tidal volume, respiratory rate, or both (Box 1.1, Equation 1). Because this pump controls $Paco_2$ levels, failure of one or more of its components can result in hypercapnic respiratory failure.

Although the respiratory pump changes minute ventilation (abbreviated as $\dot{V}_E$, because one measures *expired* minute ventilation), how those changes affect $Paco_2$ depend on associated changes in *alveolar ventilation,* $\dot{V}_A$ (Table 1.1, Equation 2). Unlike $\dot{V}_E$, which is measurable by a spirometer, $\dot{V}_A$ is a theoretic quantity that cannot be measured directly but can be illustrated if the lung is viewed as a *two-compartment model.* In this model, the lung has an alveolar space (for gas exchange) and a dead space (for convective gas flow) (Box 1.1, Equation 3). The latter includes anatomic dead space (the trachea and other conducting airways) and alveolar dead space (alveoli with ventilation/perfusion ratios [$\dot{V}/\dot{Q}$] >1.0). In this model, minute ventilation, $\dot{V}_E$, is the *sum* of alveolar ventilation, $\dot{V}_A$, and dead space ventilation, $\dot{V}_D$ (Box 1.1, Equation 4) or, alternatively, can be expressed as a function of alveolar ventilation and ratio of dead space to tidal volume (V_D/V_T) (Box 1.1, Equation 7).

If V_D/V_T and $\dot{V}_{CO_2}$ (Table 1.1, Equation 10) remain constant, P_{aCO_2} has a *hyperbolic* relationship with $\dot{V}_E$ (as the right-hand side of Equation 10 would be a constant). Figure 1.2 illustrates this relationship and how changes in $\dot{V}_E$ affect P_{aCO_2} at different values of V_D/V_T.

Respiratory Muscle Fatigue

The respiratory muscles, like any skeletal muscle, may *fatigue*—that is, become unable to produce a contraction of normal strength when stimulated by a certain neural input. Although this condition is reversible if the muscle is allowed to rest, some fatigued skeletal muscles may take up to 24 hours to recover fully to a nonfatigued state.

Acute respiratory muscle fatigue results from an *imbalance* between ventilatory capacity and "demand" for ventilation. Ventilatory capacity is represented by the maximal sustainable ventilation—that is, the maximal ventilation that an individual can maintain indefinitely without respiratory muscle fatigue developing (this is usually equal to 50% of one's maximal voluntary ventilation). The *demand* for ventilation is the spontaneous minute ventilation required to achieve the P_{aCO_2} set by the CNS controller. Increases in spontaneous minute ventilation increase the mechanical load imposed on the respiratory muscles. If this load continues to

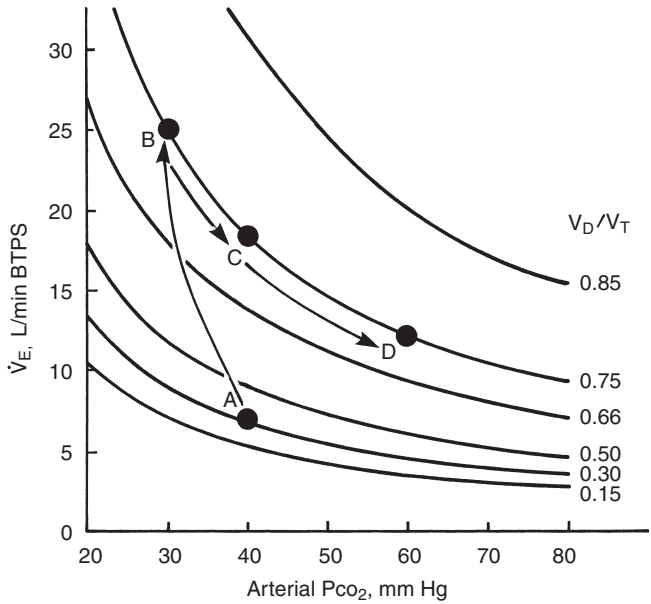


Figure 1.2 Changes in P_{aCO_2} and minute ventilation during three phases of status asthmaticus (see text for details). Isopleths of equal V_D/V_T indicate the level of minute ventilation ($\dot{V}_E$) (ordinate) that is needed to achieve a certain level of P_{aCO_2} (abscissa) for an individual with an assumed value for O_2 consumption of 200 mL/min. Normally (point A) V_D/V_T = 0.3, P_{aCO_2} = 40 mm Hg, and $\dot{V}_E$ = ~7 L/min. If V_D/V_T increases to 0.75 due to an acute asthma flare and if a new, lower value of P_{aCO_2} is used as the "set point" (P_{aCO_2} decreases from 40 mm Hg to 30 mm Hg), the patient needs to achieve $\dot{V}_E$ of ~25 L/min (point B). Point C represents the "crossover" point at which the P_{aCO_2} is normal despite $\dot{V}_E$ falling to ~18 L/min because of the onset of respiratory muscle fatigue. Finally, at point D, the patient has acute respiratory failure with elevated P_{aCO_2} despite a $\dot{V}_E$ that has decreased farther from point B or C but remains greater than at baseline (point A). *(Adapted from Selecky P, Wasserman K, Klein M, et al: Graphic approach to assessing interrelationships among minute ventilation; arterial carbon dioxide tension, and ratio of physiologic dead space to tidal volume in patients on respirators. Ann Rev Respir Dis 117:81-184, 1978.)*

increase, eventually it results in respiratory muscle fatigue unless external ventilatory support (e.g., invasive or non-invasive assisted ventilation) is provided.

At rest, a normal person has a great deal of "ventilatory reserve"; for example, one's maximal sustainable ventilation often exceeds one's resting minute ventilation by tenfold. Pathologic processes can reduce maximal sustainable ventilation while increasing the demand for ventilation. As shown in Equation 11 (Table 1.1), increased "ventilatory demand" ($\dot{V}_E$) can result either from an increase in V_D/V_T or $\dot{V}_{CO_2}$ or from a decrease in the P_{aCO_2} set point (see Figure 1.2). When ventilatory capacity approximates demand for ventilation, patients are breathing on the brink of hypercapnic respiratory failure. Further reductions in maximal sustainable ventilation or increases in demand result in an unsustainable load on the respiratory muscles and lead to *respiratory muscle fatigue.* Hypercapnic respiratory failure soon follows.

Failure of Components of the Respiratory System

As noted earlier, disorders that impair one or more component of the respiratory system can result in acute respiratory failure. In the evaluation of ICU patients with respiratory failure, identifying which of the respiratory system components has failed is essential for directing therapy. Although the effects of failure of a *single* component are described later, many patients in the ICU experience respiratory failure from the simultaneous or sequential failure of *multiple* components, and successful treatment requires taking such complexities into account.

CENTRAL NERVOUS SYSTEM COMPONENT

Acute respiratory failure arising from impaired CNS drive commonly occurs in cases of intentional overdoses of sedatives, opioids, or other drugs that can depress CNS drive—for example, tricyclic antidepressants. Iatrogenic causes arise from the therapeutic use of opioids and sedatives.

The pathophysiologic mechanism of acute respiratory failure is illustrated in Figure 1.3. Arterial blood gases typically show an acute respiratory acidosis (Table 1.1). Hypoxemia results from the effect of CO_2 retention on alveolar P_{O_2} (P_{AO_2}) (Box 1.1, Equation 12). The difference between P_{AO_2} and P_{aO_2} ($P_{(A-a)O_2}$) is the "A–a difference" (also called the "A–a gradient"). Although $P_{(A-a)O_2}$ may be normal (≤20 mm Hg when breathing ambient air) in patients with impaired CNS drive, it is often increased because of associated atelectasis (see Table 1.1). The latter develops because of small tidal volume breathing and loss of sighs (extra-large spontaneous tidal volumes).

Specific treatment includes reversing the CNS depression by giving a pharmacologic agent, if available—for example, intravenous administration of naloxone for an opioid-induced decreased respiratory drive. Many drugs that depress respiration, however, do not have effective antidotes. In these circumstances, one should intubate the patient to provide ventilation and to protect against aspiration of gastric contents (because as a rule the gag reflex is also depressed or absent).

CHEST BELLOWS COMPONENT

Respiratory muscle weakness is a common example of failure of the chest bellows component (see Chapters 48 and 67). Specific clinical disorders that produce this weakness include Guillain-Barré syndrome (acute demyelinating polyneuropathy), generalized myasthenia gravis, and cervical spinal cord injury involving the phrenic motor neurons (C3–5). Disorders of the thoracic cage and subdiaphragmatic soft tissues may also contribute to acute hypercapnic respiratory failure. Examples include acute thoracic injuries (multiple rib fractures with severe pain during breathing), certain postoperative states (after multiple rib thoracoplasty), and other mechanical limitations to

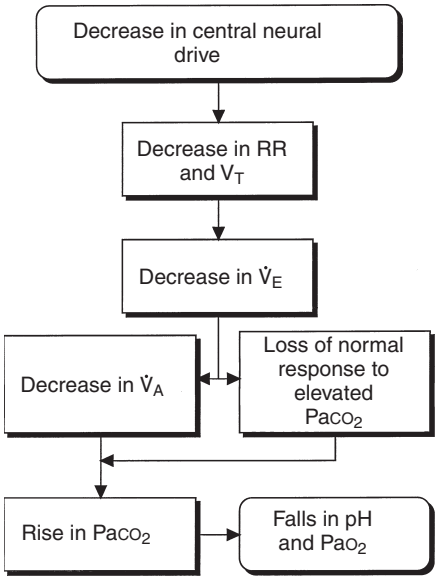


Figure 1.3 Schematic flow diagram of how impaired CNS respiratory drive results in acute hypercapnic respiratory failure. As CNS respiratory drive falls, so do respiratory rate and tidal volume. This decreases minute ventilation ($\dot{V}_E$) (see Box 1.1, Equation 1) and alveolar ventilation ($\dot{V}_A$) (see Box 1.1, Equation 8). The latter, in turn, results in a rise in P_{ACO_2} (see Box 1.1, Equation 2). In these circumstances, there is a loss of the normal response to the elevated P_{ACO_2}, which then results in acute respiratory acidosis (see Table 1.1).

TABLE 1.1 ■ **Typical Changes in Arterial Blood Gases in Acute Respiratory Failure**

Mechanism of Acute Respiratory Failure	pH	P_{ACO_2}	P_{AO_2}	Serum HCO_3	$P_{(A-a)O_2}$
Failure of central nervous system component	↓	↑	↓	WNL	WNL or ↑*
Failure of chest bellows component	↓	↑	↓	WNL	↑*
Failure of airway component					
Asthma flare					
Early phase (before respiratory failure)	↑	↓	WNL (or ↓)	WNL	↑
"Crossover point"	WNL	WNL	↓	WNL	↑
Very severe obstruction and respiratory muscle fatigue	↓	↑	↓	WNL	↑
COPD flare					
Nonchronic CO_2 retainer	↓	↑	↓	WNL	↑
Chronic CO_2 retainer					
During baseline	WNL	↑	↓	↑	↑
During flare	↓	↑↑	↓	↑	↑
Failure of alveolar component					
Before respiratory muscle fatigue	↑	↓	↓↓	WNL	↑↑
After respiratory muscle fatigue	↓	↑	↓↓	WNL	↑↑

*If atelectasis or pneumonia is present.
↑, increased; ↑↑, very increased; ↓, decreased; ↓↓, very decreased; WNL, within normal limits; COPD, chronic obstructive pulmonary disease; $P_{(A-a)O_2} = P_{AO_2} - P_{aO_2}$, where P_{AO_2} is alveolar P_{O_2}.

lung expansion (tense ascites or other disorders resulting in intra-abdominal hypertension [IAH] and its extreme form, the abdominal compartment syndrome; see Chapters 10 and 97 for more information on IAH and abdominal compartment syndrome).

The pathophysiologic mechanism of acute respiratory failure is illustrated in Figure 1.4. Neuromuscular disorders lead to acute respiratory failure primarily by limitations in ventilatory capacity (although some increase in ventilatory demand occurs because of a relatively increased V_D/V_T resulting from decreased V_T in the face of constant V_D). Although adequate CNS respiratory drive exists, transpulmonary pressures are diminished because of disruption of neuronal transmission at any point along the neuromuscular pathway from spinal cord to diaphragms or from intrinsic weakness of the respiratory muscles themselves.

These patients exhibit a pattern of small tidal volume breathing at a rapid rate, so-called rapid shallow breathing. They also cannot take large breaths or sighs. Because sighs are essential for renewing the surface tension–lowering activity of surfactant, virtually all patients who cannot take deep breaths for whatever reason (muscle weakness, pain, tachypnea) or who have their spontaneous sighs suppressed (by opioids and sedatives) experience significant microatelectasis (not visible on chest X-ray), macroatelectasis (radiographically evident as subsegmental, segmental, or lobar atelectasis), or both. Patients with neuromuscular weakness also often have poor gag reflexes and ineffective coughs and thus often develop an aspiration pneumonia too.

Arterial blood gases (ABGs) in patients with acute respiratory failure resulting from neuromuscular weakness resemble those with impaired central neural drive but usually with more

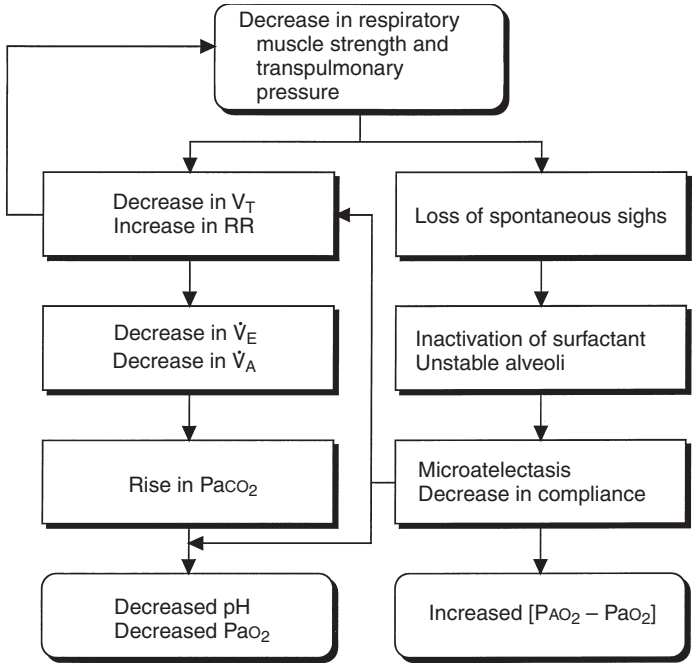


Figure 1.4 Schematic flow diagram of how neuromuscular weakness results in acute hypercapnic respiratory failure. Initially an increased respiratory rate compensates for decreased tidal volumes and maintains normal alveolar ventilation ($\dot{V}_A$) and P_{ACO_2} (mediated by the normal response to elevated P_{ACO_2}). Eventually, however, with progressive weakness, this compensation fails and P_{ACO_2} rises with an associated acute respiratory acidosis (see Table 1.1). The increase in $P(A - a)O_2$ ($P_{AO_2} - P_{aO_2}$) is due to commonly associated atelectasis, aspiration pneumonia, or both.

hypoxemia and a greater $P(A–a)O_2$ because of commonly associated atelectasis, aspiration pneumonia, or both (see Table 1.1).

Although specific therapy depends on the particular condition resulting in respiratory failure, the generic approach includes positive-pressure mechanical ventilation via tracheal intubation. Alternatively, if aspiration is not a significant concern, many patients can be effectively managed with non-invasive positive-pressure ventilation delivered via a nasal or facial continuous positive airway pressure (CPAP) mask (see Chapter 3).

AIRWAY COMPONENT

Two common examples of impairment of the airway component leading to hypercapnic respiratory failure are status asthmaticus (a severe asthma flare) and acute decompensation of chronic obstructive pulmonary disease (COPD) flare (see Chapters 75 and 76, respectively).

Pathophysiologic Mechanism of Respiratory Failure

The mechanism of CO_2 retention in both disorders is multifactorial (Figure 1.5). The capacity for ventilation decreases because of limited expiratory flow and minute ventilation as a result of airway obstruction. Airway obstruction plus a rapid respiratory rate results in dynamic hyperinflation (the cause of "auto–positive end-expiratory pressure" [auto-PEEP], also called intrinsic PEEP) (see Chapters 2 and 75). This limits minute ventilation by flattening the domes of the hemidiaphragms and compromising the normal length-force relationship of the diaphragm. These changes decrease ventilatory capacity (see Figure 1.5*A*), and other changes (see Figure 1.5*B*) increase demand for ventilation. They combine to set the stage for the development of respiratory muscle fatigue.

Arterial Blood Gases in Severe Asthma Flares

On their way to acute respiratory failure, patients with severe asthma flares often pass through *three* phases (see Table 1.1). In the *first phase*, patients have mild to moderate degrees of airway obstruction and exhibit *hypocapnia* with $Paco_2$ in the range of 30 to 33 mm Hg. This hyperventilation reflects increased respiratory input to the CNS controller from pulmonary vagal afferent receptors, for example, irritant receptors in airway epithelium, and other neural afferents stimulated by the asthma flare. This is usually accompanied by mild hypoxemia and an increased $P(A–a)O_2$ caused by a $\dot{V}/\dot{Q}$ mismatch.

In the *second phase*, as the airway obstruction becomes more severe, the respiratory muscles begin to fatigue and $Paco_2$ rises to about 40 mm Hg. Known as the *crossover point,* this "normal" $Paco_2$ is actually ominous because it represents a rise from prior *hypocapnic* levels and may indicate that respiratory muscle fatigue and hypercapnic respiratory failure are imminent. In a patient in status asthmaticus, a "normal" $Paco_2$ should definitely be considered *abnormal,* and the patient should be monitored closely for respiratory failure.

In the *third phase*, extreme airway obstruction leads to respiratory muscle fatigue and acute respiratory acidosis with an elevated $Paco_2$ (see Table 1.1). Hypoxemia is universal unless supplemental oxygen is given. Unlike COPD patients with chronic CO_2 retention, an elevated serum bicarbonate level is atypical in patients with an asthma flare because the latter typically do not have chronic CO_2 retention.

Arterial Blood Gas Changes in Chronic Obstructive Pulmonary Disease Flares

Arterial blood gases in COPD patients who are *not* chronic CO_2 retainers are similar to those observed in acute asthma flares (see Table 1.1). COPD patients with chronic CO_2 retention, however, have high serum bicarbonate concentrations at baseline because of renal compensation

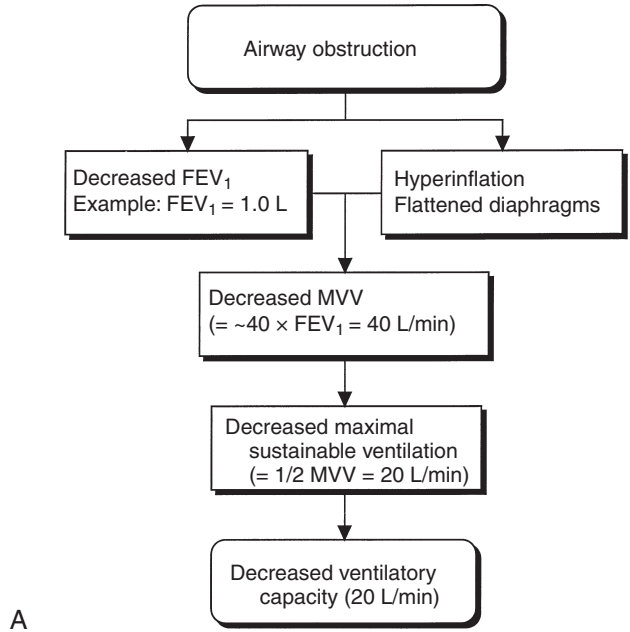


Figure 1.5 **A,** Schematic flow diagram of how airway obstruction leads to decreased ventilatory capacity. The decreased FEV_1 and mechanical disadvantage induced by flattening of the domes of the hemidiaphragms lead to a decreased maximal voluntary ventilation (MVV), which can be approximated as 40 × FEV_1. Maximal sustainable ventilation normally equals approximately 50% of MVV (although this may be increased in some patients with chronic respiratory disorders) so that a patient with severe airway obstruction as represented by FEV_1 of 1 L would have a maximal sustainable ventilation of only about 20 L/min (compared with a normal range of 100 to 200 L/min). **B,** While capacity for ventilation is falling, demand for ventilation simultaneously is increasing. This increased demand occurs because (1) CO_2 production increases (arising from increased O_2 consumption caused by the greatly increased work of breathing through obstructed airways), (2) V_D/V_T markedly increases (because of $\dot{V}/\dot{Q}$ mismatch on a microscopic level with many alveoli having $\dot{V}/\dot{Q}$ ratios > 1.0), and (3) the set point for $Paco_2$ decreases (because of vagal and other afferent stimuli to the CNS controller). The overall result of these changes as calculated by Equation 11 (see Box 1.1) shows a more than threefold increased ventilatory demand. If this demand for 25 L/min persisted in a patient whose capacity was only 20 L/min, respiratory muscle fatigue would inevitably result.

for the chronic respiratory acidosis. Acting as a buffer, the elevated bicarbonate results in a smaller fall in arterial pH as $Paco_2$ rises during an acute decompensation (see Table 1.1).

Therapy

Initial management of both asthma and COPD flares includes supplemental oxygen, inhaled bronchodilators, intravenous glucocorticosteroids, and antibiotics (if a bacterial respiratory infection is suspected) (see Chapters 75 and 76 for details). Although giving oxygen to non-intubated patients with COPD flares can worsen hypercapnia in about two thirds of cases, one should still aim to achieve adequate oxygenation in these patients. If life-threatening gas exchange and acid-base abnormalities develop, one should use positive-pressure mechanical ventilation (see Appendix B, Figures B1 and B2). Because non-invasive ventilation in patients with COPD flares has been shown to be effective and less expensive than conventional mechanical ventilation in those who tolerate it, this method of ventilation should be attempted in most patients who are still breathing spontaneously and can mobilize their respiratory secretions (see Chapters 3 and 76).

ALVEOLAR COMPONENT

Disorders that severely impair the function of the alveolar component of the respiratory system result in *hypoxemic* respiratory failure. As a rule, they also result in acute *hypercapnic* respiratory failure. These patients typically present with diffuse alveolar flooding resulting from cardiogenic or noncardiogenic pulmonary edema, diffuse pulmonary hemorrhage syndrome, or extensive pneumonia.

Hypoxemic respiratory failure occurs as a result of pathophysiologic changes in gas exchange set into motion by the alveolar flooding (Figure 1.6). Arterial blood gas measurements show

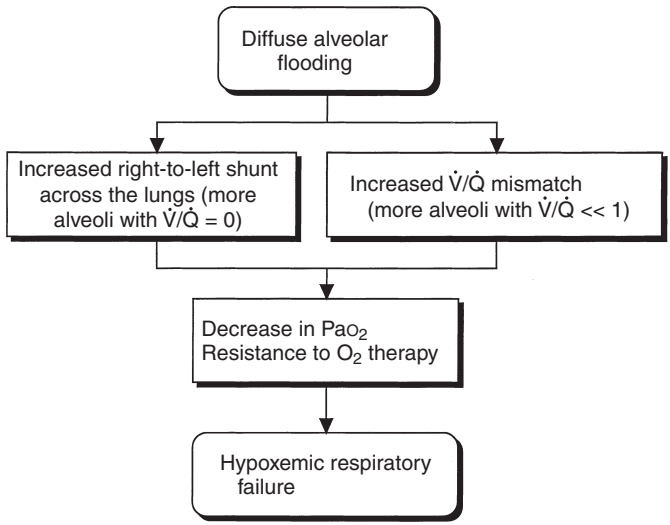


Figure 1.6 Alveolar flooding decreases ventilation to flooded alveoli to zero ($\dot{V}/\dot{Q} = 0$) or nearly zero ($\dot{V}/\dot{Q} << 1.0$). Although not an anatomic shunt, the flooded alveoli with $\dot{V}/\dot{Q} = 0$ represent a right-to-left shunt because the Po_2 of the mixed venous blood that passes through capillaries of these alveoli remains unchanged. In contrast, the alveoli with very low $\dot{V}/\dot{Q}$ represent so-called physiologic shunts because their low $\dot{V}/\dot{Q}$ results in very low alveolar Po_2. Hypoxemia due to right-to-left shunts is resistant to supplemental oxygen therapy because the supplementary oxygen does not decrease the shunt fraction.

severe hypoxemia despite the patient's breathing high concentrations of oxygen. This profound resistance to oxygen arises from the presence of a large right-to-left shunt across the lungs. Early in these disorders, *hypo*capnia and acute respiratory alkalosis are common; later, however, *hyper*-capnia occurs because of respiratory muscle fatigue (see Table 1.1). The mechanism of hypercapnic respiratory failure is multifactorial (see Chapter 73).

Therapy includes specific treatment of the causative agent (such as bacterial pneumonia) and mechanical ventilation to restore safe levels of arterial oxygenation. Large right-to-left shunt fractions should be treated by decreasing the shunt fraction (and not by giving high concentrations of oxygen alone). One does this for patients with intravascular volume overload by lowering pulmonary capillary pressure by diuresis. For patients with the acute respiratory distress syndrome (ARDS), one should lower pulmonary capillary pressure (if the patient is volume overloaded as well) and add PEEP during mechanical ventilation. If ARDS occurs as part of the syndrome of multiple organ system failure, however, one needs to balance the beneficial effects of PEEP and diuresis on improving hypoxemia with their potentially adverse effects on nonpulmonary organ dysfunction (see Chapter 73).

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CHAPTER 2

Approach to Mechanical Ventilation

Michael J. Frazer ■ Paul N. Lanken

Knowing how mechanical ventilators ventilate, their common operating modes, and the complications associated with their use is a basic but essential skill for all intensive care unit (ICU) clinicians. This chapter presents these topics, along with the physical and physiologic principles with which ICU clinicians need to be familiar in order to use mechanical ventilation rationally and safely.

The "Generic" Positive Pressure Ventilator

Virtually all ventilators used in ICUs apply *positive pressure* to the airways and lungs. For this reason, current ventilators as a class are referred to as *positive pressure ventilators*.

Although modern microprocessor-controlled ventilators have a large array of settings, controls, and displays on their consoles, all positive pressure ventilators operate by the same basic elements and parameters (Figure 2.1 and Table 2.1). The mode of ventilation selected and the patient's specific clinical circumstances should determine the exact settings.

Principles and Practice of Positive Pressure Ventilation

The effectiveness and safety of mechanical ventilation depend on numerous elements. First are the *mechanical properties* of the patient's respiratory system. Second is the *degree of synchrony* between the patient and the ventilator—that is, the interface between the patient and the ventilator. Finally, complications of positive pressure ventilation generally result from its misuse or from abnormal respiratory mechanics rather than from intrinsically damaging effects of the ventilator.

VENTILATING THE RESPIRATORY SYSTEM

The respiratory system resembles a balloon in that it inflates during inspiration, followed by passive deflation during expiration (Figure 2.2). This model has two mechanical elements: *compliance* and *resistance*. Compliance relates the gas volume in the balloon to the pressure inside the balloon under static conditions. It determines the balloon's internal pressure (static recoil pressure) after inflation to a certain volume. Resistance determines the inspiratory pressure needed to achieve a certain inspiratory airflow as well as how quickly the lungs empty during expiration.

As a rule, when adults are being mechanically ventilated via an endotracheal tube or tracheostomy tube, the respiratory system is a "closed" system and has no leaks (see Figure 2.2). Under these circumstances, the following relationship holds during inspiration:

$$P_{prox} = \Delta P_{AW} + P_{ALV} = [R(airways) \times flow] + P_{ALV} \qquad \text{(Equation 1)}$$

where Pprox is the pressure at the proximal end of the artificial airway during inspiration; ΔP_{AW}, the pressure drop across the airways during inspiration; R(airways), airway resistance; flow, the inspiratory flow rate; and P_{ALV}, the alveolar pressure during inspiration.

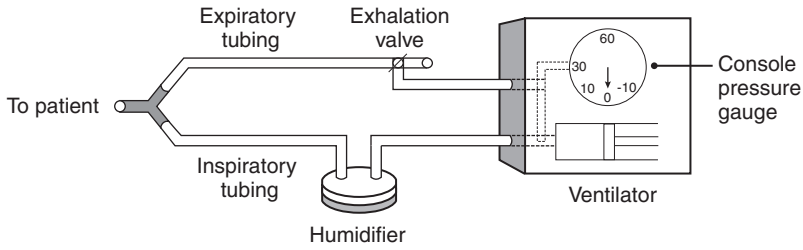


Figure 2.1 Model of Basic Elements of a Volume-Cycled Ventilator. The ventilator delivers a preset tidal volume (symbolized by the piston and cylinder) via the inspiratory tubing and humidifier to the patient. The exhalation valve is closed by positive pressure during inspiration. At the start of exhalation, the valve opens and the expired gas exits the circuit via the expiratory tubing (normally the exhaled gas reenters the ventilator to monitor its volume). The pressure gauge on the console reflects pressure proximal to the inspiratory tubing. *(Modified from Lanken PN: Mechanical ventilation. In Fishman AP [ed]: Pulmonary Diseases and Disorders, 2nd ed. New York: McGraw-Hill, 1988.)*

TABLE 2.1 ■ **Basic Ventilator Parameters and Typical Initial Settings**

Parameter	Settings	Range	Comments
Mode	A/C		Use A/C mode for patients not breathing spontaneously and for starting assisted ventilation
Respiratory rate	8–12 BPM*	5–35 BPM	For patients without spontaneous breathing efforts, set rate to achieve a desired $Paco_2$ guided by ABGs
			For spontaneously breathing patients in A/C or IMV mode, set rate 2–3 BPM below spontaneous rate
Tidal volume	400–600 mL*	400–800 mL	For patients with ARDS or at risk for ARDS, low tidal volumes (i.e., 6 m/kg predicted body weight [PBW]) are recommended†
F_{IO_2}	1.0	0.21–1.0	Start at 1.0 and taper as guided by Pa_{O_2} or Sa_{O_2}
Inspiratory flow rate	60–70 L/min	50–100 L/min	Flows are set higher when patient has a high respiratory rate or "air hunger" or to decrease inspiratory time
I:E ratio	1:2	2:1 to 1:4	Usually a derived, not a preset, parameter

*Initial settings for 70-kg PBW adult with normal lungs (see Appendix E for tidal volumes based on PBW for men and women). Set initial rate higher than 8 to 12 BPM if lung disease is present—for example, asthma and COPD, depending on the disease (see Appendix B for more considerations of dead space).

†See Appendix E.

ABGs, arterial blood gases; A/C, assist/control; ARDS, acute respiratory distress syndrome; BPM, breaths per minute; F_{IO_2}, fractional concentration of inspired oxygen; PBW, predicted body weight; I:E, inspiratory time to expiratory time; Pa_{O_2}, partial pressure of oxygen in arterial blood; Sa_{O_2}, arterial O_2 saturation; IMV, intermittent mandatory ventilation; COPD, chronic obstructive pulmonary disease.

Equation 1 indicates that the proximal airway pressure during inspiration is the sum of two components: (1) a dynamic component, ΔP_{AW}, representing the pressure drop that occurs as air flows into the lungs (as a result of the resistance of artificial and natural airways), and (2) a static component, P_{ALV}, the mean pressure in alveoli, which represents the static recoil pressure of the lungs and chest wall. This pressure is determined by the increase in lung volume above functional residual capacity (FRC), the volume in the lungs at end expiration.

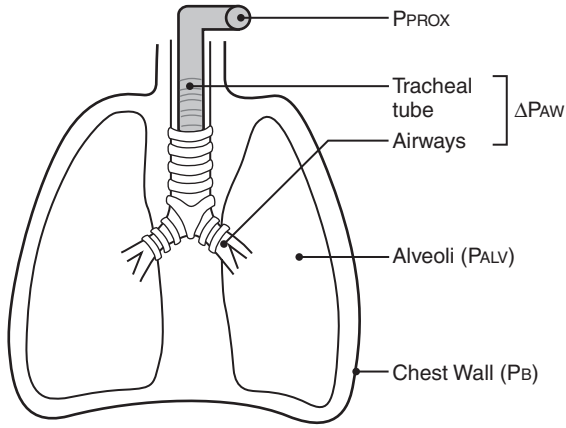


Figure 2.2 The respiratory system (lungs plus chest wall) is a closed system during ventilation with a cuffed endotracheal tube. See Equation 1 for relationships among pressures. Pprox, pressure at proximal end of endotracheal tube; ΔPAW, pressure drop across airways during inspiration as a result of resistance of artificial and natural airways; PALV, alveolar pressure (equal to the static recoil pressure of the respiratory system); PB, barometric pressure. *(Modified from Lanken PN: Mechanical ventilation. In Fishman AP [ed]: Pulmonary Diseases and Disorders, 2nd ed. New York: McGraw-Hill, 1988.)*

PRESSURE-VOLUME CURVES OF THE RESPIRATORY SYSTEM

Static Pressure-Volume Curve

As noted earlier, changes in lung volume above FRC during inspiration relate to the recoil pressure of the respiratory system (Figure 2.3*A*). The *compliance of the respiratory system* incorporates both lung compliance and chest wall compliance and is expressed as follows:

$$Cstat = \Delta V/\Delta P \qquad \text{(Equation 2)}$$

where Cstat is the static compliance of the respiratory system, ΔV is a change in volume, and ΔP is the corresponding change in pressure.

In general, ΔP equals the plateau pressure (Pplat) minus the end-expiratory pressure (which equals zero unless positive end-expiratory pressure [PEEP] is present). One measures Pplat as the airway pressure after a certain tidal volume has been delivered by use of an inspiratory pause (0.5-second pause) at end inspiration. While monitoring Cstat over time, one should use the same tidal volume for each Pplat measurement. Normal respiratory system compliance is 50 to 100 mL/cm H_2O—that is, the lungs and chest wall expand by 50 to 100 mL for every 1 cm H_2O of static distending pressure. *Decreased* respiratory system compliance is common in ICU patients and, if present, needs special consideration during ventilator management. Such a Cstat indicates that the respiratory system is "stiffer" than normal. This may be due to stiff lungs, such as those caused by pulmonary edema, or a stiff chest wall, resulting from edema of the chest wall or taut, dilated loops of bowel encroaching into the chest.

A *high* Cstat usually does not affect ventilator care as much as a low Cstat. A high Cstat may reflect abnormal lungs that have lost their elastic recoil because of emphysema or an abnormal chest wall that has low compliance, such as that caused by neuromuscular blocker–induced paralysis or multiple rib fractures and a "flail chest."

Dynamic Pressure-Volume Curve

The *static* pressure-volume (P-V) curve of the respiratory system, discussed earlier, applies only when there is no airflow—that is, at end inspiration or end expiration. When air is flowing into or

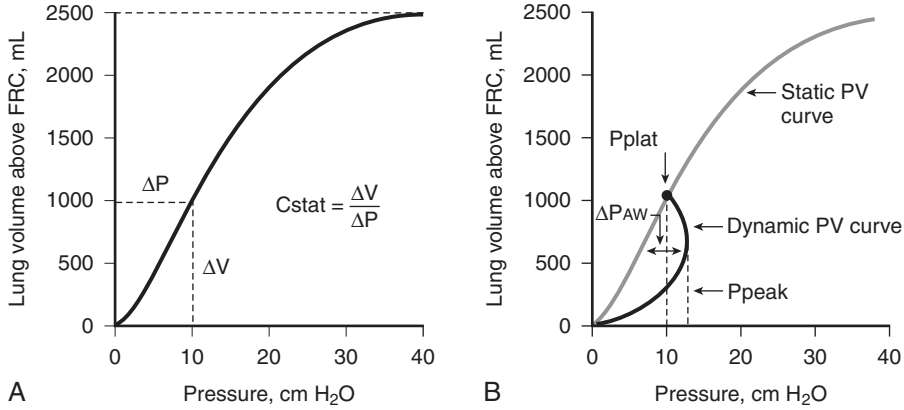


Figure 2.3 Schematic Pressure-Volume (P-V) Curves of the Respiratory System, with the Static Recoil Pressure of the Respiratory System (P_{ALV} in Figure 2.2) as Abscissa. **A,** Static P-V curve. A tidal volume of 1000 mL results in recoil pressure of 10 cm H_2O. Because compliance of the respiratory system (Cstat) is equal to the change in volume (ΔV) above functional residual capacity (FRC) divided by the change in pressure (ΔP), Cstat = (1000 mL/10 cm H_2O) = 100 mL/cm H_2O (a normal value). Note that the curve flattens at higher pressures as total lung capacity is approached. **B,** Dynamic P-V curve of 1000 mL tidal volume superimposed on the static P-V curve in *A*. The difference between the two curves (ΔP_{AW}) represents the pressure drop across the airways resulting from airway resistance. Note that peak pressure (Ppeak) exceeds the end-inspiratory static pressure (plateau pressure or Pplat) by ~2 cm H_2O, reflecting normal airway resistance. *(Modified from Lanken PN: Mechanical ventilation. In Fishman AP [ed]: Pulmonary Diseases and Disorders, 2nd ed. New York: McGraw-Hill, 1988.)*

out of the lung, resistance to airflow comes into play as can be seen by the patient's dynamic P-V curves (see Equation 1 and Figure 2.3*B*).

Basic Traditional Modes of Ventilation

All ventilators used in the ICU setting can provide three basics modes of ventilation: (1) assist/control (A/C) mode, (2) pressure support (PS) mode, and (3) intermittent mandatory ventilation (IMV) mode. Most microprocessor-controlled ventilators can provide additional alternative modes of assisted ventilation, several of which are discussed later in this chapter.

ASSIST/CONTROL MODE

The term *assist/control mode* arises from two traditional methods of ventilation used in early ventilators: (1) assist mode, which allows a patient with spontaneous breathing efforts to initiate the desired machine-delivered tidal volume, and (2) control mode, which provides machine breaths without regard to the patient's pattern of breathing. The latter is now obsolete because it "locks out" patients even if they are making spontaneous efforts to breathe. Furthermore, studies have indicated that total lack of use of the respiratory muscles rapidly leads to disuse atrophy. This can be prevented, in part, by providing neural stimuli for muscular contractions (e.g., those provided by the assist mode), even if the ventilator provides most of the work of breathing.

Settings

The *control mode* is straightforward because the operator sets only two primary parameters: respiratory rate and tidal volume (Figure 2.4*A*). Most ventilators function as *volume-cycled ventilators*, in

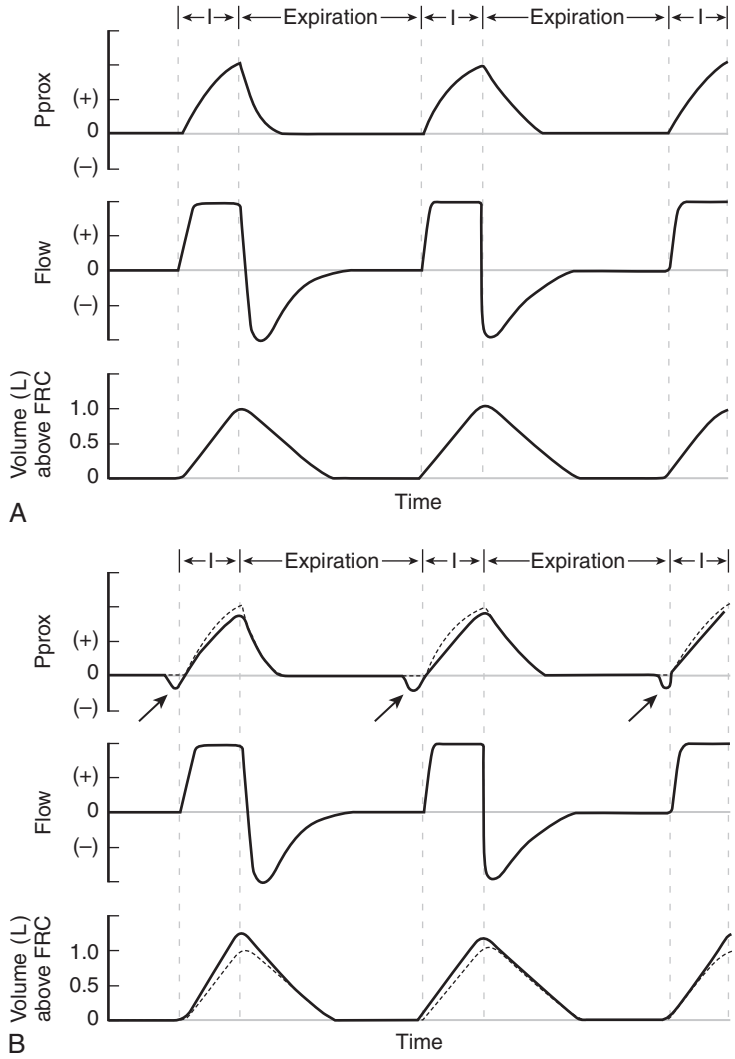


Figure 2.4 Schematic Pressure, Flow, and Volume Waveforms vs. Time in Control and Assist Modes. **A,** Control mode. Flow is delivered as a square wave during inspiration. During this mode, the patient makes no spontaneous efforts to breathe. Note that the tidal volume is 1 L. **B,** Assist mode. Each inspiration is triggered by the patient's spontaneous breathing effort *(arrows)*. Note that the pressure waveform is distorted from the control mode *(dashed curves)* because of the patient's continued efforts to breath during inspiration. Also note that the delivered tidal volume is greater than the 1 L delivered previously in the control mode *(dashed curves).* This is because the patient's continued inspiratory efforts took additional volume from the ventilator's demand valve. Pprox, pressure at proximal end of endotracheal tube; FRC, functional residual capacity; I, inspiration; (+), inspiratory flow; (–), expiratory flow.

which inspiration ceases after the preset tidal volume is delivered to the patient. Unless there is a leak in the system, such as around the cuff of a tracheal tube or through a chest tube, or unless peak inspiratory pressure exceeds the "pop-off" pressure (the threshold set for the peak pressure alarm [see Chapter 47]), the patient should receive all of the preset tidal volume. The combination of rate and tidal volume, therefore, defines the minute ventilation that the patient receives (Table 1.1).

The *assist mode* adds two features of operation to the control mode (Figure 2.4*B*). First, the ventilator can detect a patient's inspiratory effort (by detecting the negative pressure deflection from baseline in the inspiratory circuit or by detecting the beginning of patient-initiated airflow through the ventilator's demand valve). When that inspiratory effort exceeds a certain threshold, the patient "triggers" the ventilator to begin delivery of the preset inspiratory tidal volume. The timing of the start of the next inspiration is defined by the set respiratory rate or by the patient's spontaneous rate, whichever is higher. For example, if the preset rate is 10 breaths/min, the ventilator provides a tidal volume every 6 seconds unless it detects the patient's spontaneous inspiratory effort earlier. If it does, it resets the start of the next ventilator-initiated breath to be 6 seconds from the start of the patient-initiated breath.

The second additional feature of the assist mode allows the patient to inspire from the ventilator's demand valve (which is similar to the demand valve of SCUBA [self-contained underwater breathing apparatus] gear). This occurs during inspiration if the patient's inspiratory flows exceed those generated by the ventilator or if the patient continues to inspire after the preset tidal volume has been delivered. In this manner, the patient's actual tidal volumes can be consistently larger than the ventilator's set tidal volume (see Figure 2.4*B*). On occasion, patients breathing vigorously can also set off the ventilator's low inspiratory pressure alarm by continually inspiring during machine inspiration (see Chapter 47 for more information about alarms).

Mechanical Considerations

In volume-cycled ventilation, such as in A/C mode, the delivered tidal volume is less than the preset tidal volume if the peak inspiratory pressure (PIP) exceeds the threshold for the peak pressure alarm. For any given tidal volume and inspiratory flow rate, PIP is determined by two factors relating to the patient's mechanics (as expressed in Equations 1 and 2): airway resistance and static compliance of the respiratory system. If the PIP exceeds the threshold for the ventilator's peak pressure alarm, the remaining tidal volume is "dumped" (allowed to escape from the system) and is not delivered to the patient. This may occur if the patient actively resists the machine-delivered inspiration (termed *bucking* or *fighting* the ventilator) or coughs (both of which decrease compliance of the respiratory system). Another common cause of high PIPs is if the patient's airway resistance increases, such as in an airway that is partially blocked by respiratory secretions or by the patient biting the endotracheal tube.

Clinical Considerations

The A/C mode of ventilation is indicated for patients without spontaneous respiratory efforts, such as in paralyzed and apneic patients, or for patients with potential loss of their breathing efforts. The latter include patients with drug overdoses that wax and wane in their depressive effects on central nervous system respiratory drive. It is also the mode of choice to provide therapeutic hyperventilation.

Numerous studies have indicated that spontaneously breathing patients with a high ventilatory drive often continue to have a high work of breathing while on A/C mode. In these conditions, they may make strenuous efforts to breathe during machine-delivered inspirations, as reflected by negative esophageal pressure swings during machine inspiration. As a consequence, if such patients were put on A/C mode because of respiratory muscle fatigue, this mode may not effectively "unload" their respiratory muscles—that is, put their respiratory muscles at rest to allow for full recovery from skeletal muscle fatigue.

In the case of patients who have high respiratory rates while on A/C mode, one must first check that the ventilator's triggering sensitivity is not excessive (which could lead to ventilator self-cycling and high respiratory rates). One can address the problem of ventilated patients who

continue to make strong inspiratory efforts on A/C mode by increasing inspiratory flow rates and checking for auto-PEEP (auto–positive end-expiratory pressure, described later). If auto-PEEP is present, it should be treated as discussed later. If the tachypnea persists, one may need to suppress the patient's high respiratory drive pharmacologically, such as with more sedation (see Chapter 5), in order to provide a respite for the patient's respiratory muscles. Changing to the PS mode of ventilation is another alternative.

PRESSURE SUPPORT MODE

Pressure support mode differs from the A/C mode in how it provides assisted ventilation. Instead of delivering a preset tidal volume, PS delivers a preset pressure. When it detects that the patient is starting to inhale, it provides a certain level of pressure to the inspiratory circuit. The result is a synchronized inspiratory pressure "boost" that assists the patient's own efforts in order to augment the patient's spontaneous tidal volume and to unload the patient's respiratory muscles (Figure 2.5*A*). The boost stops when the ventilator detects that inspiratory flow has decreased to a certain degree.

Settings

One should set the level of PS to achieve a certain tidal volume during the patient's spontaneous breathing. Often, a trial-and-error approach is used to arrive at the appropriate level of PS. The respiratory rate is the patient's spontaneous respiratory rate. Backup minute ventilation is available on modern ventilators as a safety feature if patients stop or slow their breathing or if tidal volumes fall because of fatigue or changes in lung mechanical properties.

Mechanical Considerations

As noted earlier, tidal volumes in PS may fall if the mechanical properties of the patient's respiratory system change or the patient's respiratory muscles become fatigued. Instead of delivering a certain preset tidal volume, as in A/C or IMV mode, PS provides only the desired level of pressure support during a patient-initiated inspiration. What size tidal volume this pressure generates depends on the inspiratory effort, the duration of the inspiratory flow, the airway resistance, and the respiratory system compliance. If any of these factors fluctuate over time, tidal volumes at the same PS also fluctuate. In addition, the respiratory rate on PS is the patient's *spontaneous* respiratory rate. Because this may also change over time, the need for backup ventilation should be self-evident. Certain ventilators can provide a backup ventilation when they detect an exhaled minute ventilation lower than threshold setting.

Clinical Considerations

As noted earlier, ICU clinicians set the level of inspiratory pressure support, not a certain tidal volume or respiratory rate. Because tidal volumes may change at the same selected level of PS as a result of changes in airway resistance and Cstat, PS is less attractive when these mechanical properties are expected to fluctuate, such as in acute asthma flares. Likewise, PS mode is problematic when apneas or hypopneas occur or when giving sedation for procedures. If the PS mode is used in these conditions, having a backup mode of ventilation is necessary.

INTERMITTENT MANDATORY VENTILATION MODE

The IMV mode consists of two types of ventilation (Fig. 2.5*B*). The first type of ventilation in synchronized IMV is identical to that in A/C mode, and it provides machine-delivered tidal volumes at a preset respiratory rate. In current ventilators, these IMV breaths are synchronized with

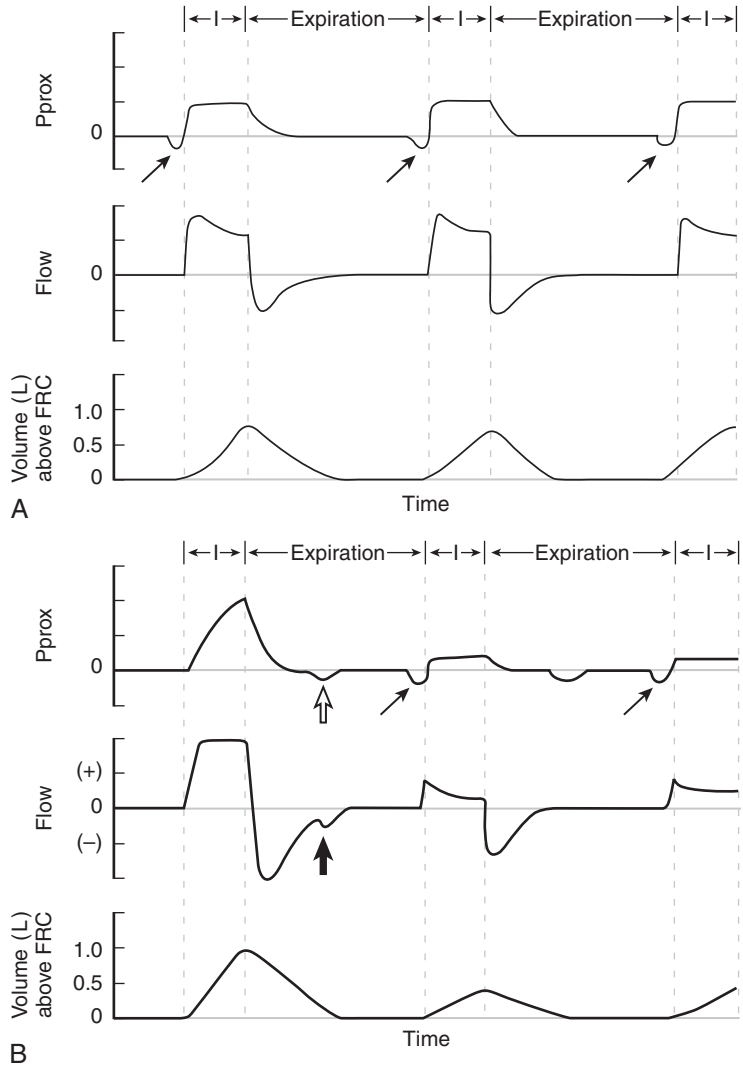


Figure 2.5 Schematic Pressure, Flow, and Volume Waveforms vs. Time in Pressure Support (PS) and Intermittent Mandatory Ventilation (IMV) Modes. **A,** PS mode. Patient triggers each breath *(arrows)*, resulting in a pressure assist during inspiration, which results in a tidal volume of 0.75 L. **B,** IMV mode. The first breath is a machine-delivered tidal volume of 1 L, not triggered by the patient. The second breath, 0.5 L, represents the patient's spontaneous breath (enhanced by a low level of PS). The *vertical open arrows* indicate two inspiratory efforts that were not sensed by the ventilator. Note that the first of these *(solid vertical arrow)* distorts the expiratory flow waveform (compare with Figure 2.4*A* or 2.4*B*). FRC, functional residual capacity; Pprox, pressure at proximal end of endotracheal tube; I, inspiration; (+), inspiratory flow; (–), expiratory flow.

the patient's spontaneous breaths so that they do not "stack" on top of the patient's spontaneous breaths. The second type of ventilation allows the patient to breathe spontaneously from the ventilator's demand valve. The volume and the rate of these spontaneous breaths depend on the patient's respiratory drive, the level of PS applied to the spontaneous breath (which is the usual practice), and the mechanical properties of the patient's respiratory system.

Settings

The primary settings for IMV mode include IMV rate and tidal volume. In addition, to compensate for the airway resistance of the artificial airway, a low level of pressure support (5 to 8 cm H_2O) is often added to aid the spontaneous breaths (see Figure 2.5*B*).

Mechanical Considerations

As in the A/C mode, the operator sets the IMV tidal volumes. Their corresponding peak inspiratory pressures are also determined by the mechanical properties of resistance and compliance.

Clinical Considerations

Although synchronized IMV was originally developed as a weaning mode from mechanical ventilation, some ICU clinicians use synchronized IMV as their standard mode of mechanical ventilation, weaning or not. This practice probably reflects the style of their institution or clinical training. Because of a lack of studies comparing outcomes of patients ventilated with A/C mode or IMV under nonweaning conditions, there are no data indicating which mode results in better outcomes. In the absence of compelling results to the contrary, either mode can be used successfully for assisted ventilation, but one mode may be better than the other in some circumstances.

For example, for patients with respiratory muscle fatigue, some clinicians have expressed concern that even though IMV rates provide for adequate CO_2 removal, they may be set too low to provide adequate unloading of the respiratory muscles. In addition, as discussed in Chapter 4, the two classic clinical trials comparing methods of weaning indicated that IMV was the *slowest* weaning method. IMV has a physiologic advantage over A/C mode, however, when there is auto-PEEP (intrinsic PEEP). The patient's spontaneous breaths in IMV provide negative intrathoracic pressures that counterbalance the positive intrathoracic pressure of the auto-PEEP and IMV breaths.

Some ICU clinicians use IMV when they encounter patients with hyperventilation and a severe respiratory alkalosis. These patients breathe at high respiratory rates on A/C mode because of an increased central nervous system (CNS) respiratory drive. Simply switching the patient from A/C to IMV mode does not solve the problem of alkalosis unless the patient's respiratory muscles become fatigued during IMV. This is clearly not a desirable outcome. Likewise, adding extra dead space or locking out the patient (by setting the triggering threshold high) should not be used, because both methods may also induce respiratory muscle fatigue. Under these conditions, it is more appropriate to decrease the patient's high CNS drive pharmacologically, such as with anxiolytics if the high rates are due to anxiety, opioids, or even paralysis for other states of centrally mediated hyperventilation (see Chapters 5 and 6).

NON-INVASIVE VENTILATION

Non-invasive ventilation has established itself as a safe and effective approach for many patients with acute or chronic respiratory failure. For some, such as those with obesity-hypoventilation syndrome, it is the method of choice for assisted ventilation (see Chapter 80). Chapter 3 describes use of non-invasive ventilation in the ICU in detail.

Alternative Closed Loop Modes of Ventilation

Closed loop modes of ventilation are available on recent generations of mechanical ventilators. Closed loop ventilation requires the microprocessor of the ventilator to automatically adjust its output based on certain measured parameters. Among these are pressure regulated volume control (PRVC), volume support (VS), proportional assist ventilation (PAV), and neurally adjusted ventilatory assist (NAVA). Although these modes have different names depending on which ventilator is being used, the operational algorithms are similar.

PRESSURE REGULATED VOLUME CONTROL (PRVC OR VC PLUS [VC+])

Pressure regulated volume control (PRVC or VC+) is often referred to as a dual mode. It delivers an A/C type breath via constant (square) pressure with a fixed inspiratory time but with variable inspiratory flow in a decelerating pattern to achieve a targeted tidal volume based on the patient's inspiratory demand, dynamic compliance, and airway resistance. The inspiratory pressure will adapt to the inspiratory demand and lung mechanics of the patient. Typically, the initial breath is delivered at a minimal predetermined pressure to determine lung compliance, followed by several more test breaths to determine the calculated inspiratory pressure required to deliver the target tidal volume. PRVC may cause delays in reestablishing ventilation after disconnect.

PRVC is generally utilized to maintain the lowest possible airway pressure and to match the patient's inspiratory flow demands while delivering the desired tidal volume.

Settings

The settings for PRVC are a combination of assist and pressure control, including tidal volume, respiratory rate, F_{IO_2}, inspiratory time, rise time, PEEP, and pressure or flow sensitivity. PRVC/SIMV, available on most model ventilators with PRVC, also incorporates pressure support and expiratory sensitivity.

Mechanical Considerations

One consideration with PRVC is that, due to this pressure regulation, a sustained high inspiratory demand can cause the ventilator to respond with an inappropriate decrease in peak inspiratory pressures (PIP, mean airways pressure [MAP]). However, this change is not indicative of improving compliance, thus contributing to patient-ventilator asynchrony, and inappropriately increased tidal volumes.

Clinical Considerations

Inappropriate setting of PRVC can result in poor synchrony between patient and ventilator. Consequently, alarm settings are important when utilizing PRVC. The high inspired tidal volume limit alarm enables the practitioner to control delivered volumes, thus preventing volutrauma. The pressure limit alarm prevents the ventilator from delivering inappropriately high inspiratory pressure to achieve the set target volume. Setting this alarm 10 cm H_2O above the pressure required to deliver the target volume helps to achieve this goal. The alarm sounds to alert the practitioner when the PIP reaches 5 cm below the alarm setting.

In pressure control (PC), the practitioner sets an inspiratory pressure, PEEP, and inspiratory time. Hence, the PIP is equal to Pplat at the point of inspiratory flow termination. In PRVC, the practitioner sets PEEP, inspiratory time, and a target tidal volume. In contrast to PC, PRVC delivers a variable inspiratory pressure to achieve the target volume; therefore, inspiratory pressures and set inspiratory time should be monitored closely to prevent Pplat from exceeding 30 cm H_2O. Similar to PC, the inspiratory pressure is constant (square) during the set inspiratory time.

If the patient is receiving a low tidal volume (lung protective) ventilatory strategy (e.g., as treatment for the acute respiratory distress syndrome [ARDS]), then PRVC may increase the delivered tidal volume above the set tidal volume of 6 mL/kg predicted body weight (PBW).

If the patient is air trapping (also referred to as dynamic hyperinflation, which results in auto-PEEP—described later in this chapter), expiratory volume will be less than previously measured, and the ventilator will augment inspiratory pressure to deliver more volume on the next delivered breath. As this cycle continues, intrinsic PEEP levels (auto-PEEP) increase, risking barotrauma, high PIP and Pplats, and possible hemodynamic instability. In patients with air leaks (e.g., a bronchopleural fistula), the ventilator continues to increase inspiratory pressure in an attempt to

deliver the target tidal volume. If the ventilator is unable to reach such a pressure, then PRVC mode cannot start up and it will continue to cycle without ventilating the patient.

VOLUME SUPPORT (VS)

Volume support is a spontaneous mode of ventilation. The target support volume is a pressure-supported breath. Similar to PRVC (VC+), VS delivers a pressure-based breath to achieve a target tidal volume set by the practitioner. The pressure support can vary breath to breath to achieve the target tidal volume based on changes in resistance, compliance of the circuit, airway or lungs, or inspiratory effort.

Settings

The settings for VS are target support (tidal) volume, rise time % and expiratory sensitivity, PEEP, and FIO_2. The practitioner does not determine a pressure support setting during VS.

Considerations

This particular mode has not received the attention or usage PS has due to a lack of supporting evidence. One possible advantage is the avoidance of the tidal volume swings that occur in pressure support ventilation.

Weaning of the patient from the ventilator is followed by the peak inspiratory pressure (PIP). Peak pressure will decrease as the ventilator delivers less support pressure (PIP-PEEP) while the patient recovers.

Careful attention to peak pressure as compliance or resistance worsens is advised to prevent undesirable levels of support pressure being delivered. Proper knowledge of settings and alarms are essential prior to implementing this mode of ventilation.

PROPORTIONAL ASSIST VENTILATION PLUS (PAV+)

Proportional assist ventilation plus (PAV+) is a spontaneous mode of mechanical ventilation characterized by the delivery of a variable airway pressure continuously adjusted to match the work of breathing (WOB) required by the patient for inspiration. An addition to the PAV algorithm (PAV+) allows the frequent measurement of both elastance and resistance, enabling continuous adjustments of inspiratory support in response to changes in patient airway, lung, and chest wall mechanics.

Settings

The primary PAV+ settings are percentage support (i.e., the ventilator supplied support), tube type, and tube internal diameter (I.D.). The percentage support range is 5% to 95%. If percentage support is increased, the degree of ventilator support will increase, thus decreasing the patient's WOB. Conversely, if percentage support is decreased, the degree of ventilator support will decrease, thus increasing the patient's WOB.

Mechanical Considerations

One consideration for PAV+ is setting the correct size and type of artificial airway due to the resultant under-supporting or over-supporting of the patient by entering incorrect information For instance, entering a smaller than actual artificial airway could result in over-supporting the patient by delivering larger tidal volumes and vice versa. Another consideration for PAV+ is if the ventilator cannot accurately measure airway resistance and lung compliance, PAV+ will not be able to initiate. This could be caused by a leak in the circuit or by a patient who has no respiratory effort.

Clinical Considerations

One of the differences and possible advantages of PAV+ over other modes of ventilation is that PAV+ provides a level of support that is proportional to both the respiratory impedance and respiratory drive of the patient. Other modes of ventilatory support provide a fixed level of inspiratory assistance. An important feature of PAV+ is the ability to adjust the fraction of the required WOB performed by the patient or by the ventilator, which is done by setting a gain factor (percentage support) on the ventilator. With minimal gain, the patient performs most of the WOB, whereas the ventilator performs most of the required WOB at higher gain settings.

Specific information including the measurement of inspiratory flow and lung volume every 5 milliseconds, consistent resistance, and compliance measurements every 4 to 10 breaths enable the ventilator to deliver this proportional support in PAV+. An additional prerogative of PAV+ is that it does not excessively increase tidal volume above a patient's spontaneous levels; rather, it facilitates a decrease in the patient's WOB at a relatively constant tidal volume and respiratory rate maintaining unaltered the patient's respiratory pattern. PAV+ may reduce WOB to be within the physiologic range. Additionally, PAV+ may achieve tidal volumes that are consistently within the range for a lung-protective ventilatory strategy.

Finally, PAV+ may improve the interaction between patient and ventilator, decrease respiratory drive, and minimize dynamic hyperinflation. PAV+ is not intended for use with non-invasive ventilation, tracheal cuffs, or breathing circuits with leaks. It should also be noted that PAV+ is designed for patients with a stable inspiratory drive.

NEURALLY ADJUSTED VENTILATORY ASSIST (NAVA)

Neurally adjusted ventilatory assist (NAVA) is a new spontaneous mode of ventilation found on the SERVO-i ventilator in which the support pressure is delivered via a neural trigger or a pneumatic trigger. NAVA detects the diaphragmatic electrical activity (Edi) in the beginning stages of the inspiratory effort, whereas conventional ventilation detects efforts of the patient at a later stage.

Settings

If the ventilator senses a neural trigger, the following settings are active: NAVA level, PEEP, FIO_2, and Edi trigger. Subsequently, a secondary trigger based on flow or pressure triggering utilizes these settings: trigger level, inspiratory cycle off, and pressure support level above PEEP.

Considerations

NAVA feeds the detected diaphragmatic electrical activity (Edi) to the ventilator and in synchrony delivers assist through support pressure in proportion to the patient's measured Edi in real time. A nasogastric tube referred to as an Edi catheter detects the Edi.

Consequently, NAVA's ability to deliver real-time support pressure may promote synchrony and comfort between the patient and the ventilator. It can deliver physiologic tidal volumes in accord with low tidal volume lung protective ventilation and may decrease the need for deep sedation.

Similar to PAV, the ventilator will decrease or increase delivered support based on the patient's condition.

Studies are under way to determine the efficacy and possibilities of this mode compared to traditional modes of ventilation.

Patient Management during Mechanical Ventilation

MONITORING AND ALARMS

Monitoring patients receiving mechanical ventilation is essential to their safe management. This monitoring takes many forms that anticipate potential problems related to (1) the intrinsic function

of the ventilator, (2) the ventilator-patient interface, and (3) the patient's physiologic status. These are discussed more fully in Chapter 47.

Dyssynchrony between Patient and Ventilator

Lack of synchrony between the patient and the ventilator in terms of breathing patterns is probably the most common complication of mechanical ventilation. Usually, the patient is dyspneic and struggling to breathe so that lack of synchrony between patient and ventilator means continued respiratory distress for the patient and a possibly increased risk of barotrauma. Dealing with interface problems between the patient and the ventilator is more of an art than a science once physiologic causes of the distress, such as hypercapnia and hypoxemia, are ruled out. Experienced respiratory care practitioners and ICU nurses should be sought for guidance in making ventilator adjustments and in calming the distressed patient by reassurance or medications. Because most patients receiving invasive ventilation are receiving sedatives, these can be increased in dosage, if necessary, to improve synchrony between the patient and the ventilator (see Chapter 5).

COMPLICATIONS OF MECHANICAL VENTILATION

A host of complications are associated with intubation and mechanical ventilation (Box 2.1).

Patient Dysphoria

Having an endotracheal tube in one's trachea, feeling suffocated from secretions that need suctioning, or enduring painful sensations during suctioning are unpleasant and

BOX 2.1 ■ Complications of Mechanical Ventilation

Gas Exchange Problems

Acute respiratory alkalosis due to overventilation of patients with chronic CO_2 retention*
Hyperventilation, including ventilator "self-cycling" due to sensitivity being set too low
Hypoventilation, especially due to cuff leaks or inappropriate settings or mode
Hypoxemia due to atelectasis (secretions, lack of turning, or tube malposition)

Tube Problems

Intubation of right main branches
Excessive airway resistance due to kinking, clogging, and so on
Self-extubation
Tracheomalacia due to excessive cuff pressures (> 25 cm H_2O) (see Chapters 22 and 30)

Other Problems

Auto-PEEP with hypotension
Barotrauma, including tension pneumothroax
Dysphoria (due to endotracheal tube and suctioning)
Microatelectasis and macroatelectasis
Nosocomial pneumonia
Sodium and water retention†
Ventilator-induced lung injury (VILI) (see Chapter 73)

PEEP, positive end-expiratory pressure.
**See more details of this complication and how to avoid it in Appendix B.*
†Sodium and water retention is believed to occur primarily through the effects of positive pressure ventilation that decreases cardiac output and renal perfusion, but a decrease in the secretion of atrial natriuretic factor may also play a role.

frightening experiences for awake and alert ICU patients on mechanical ventilation. These are in addition to the pain, fear, and other physical and emotional discomforts caused by their underlying conditions or their other ICU interventions. For these reasons, virtually all noncomatose patients on ventilators are treated with medications for dysphoric sensations, such as benzodiazepines for anxiolysis, sedation, and amnesia and opioids for sedation and analgesia (see Chapter 5).

Auto-PEEP (Intrinsic PEEP)

DEFINITION AND DETECTION

Auto-PEEP ("intrinsic PEEP") is defined as the presence of positive alveolar pressure at the start of a new inspiration that is not due to applied PEEP (Figure 2.6). Levels of auto-PEEP can range from trivial (1 to 2 mm Hg), with no adverse effects, to substantial (> 20 mm Hg), causing severe, life-threatening problems. It has also been called "occult PEEP" because it does not appear on the pressure gauge of the ventilator (Figure 2.6*C*). Its presence, however, can be reliably inferred by inspection of the ventilator's display of waveforms for pressure and flow (Figure 2.7). Some degree of auto-PEEP is present in all patients with airway obstruction when receiving mechanical ventilation.

Certain ventilators can measure auto-PEEP in spontaneously breathing patients by using a shutter valve that activates at the end of expiration and then measures the pressure in the tubing circuit after it equilibrates with alveolar pressure. One can also estimate its magnitude by making a well-timed occlusion of the expiratory port just before the start of inspiration on some ventilators, although this is not recommended for routine practice. (Figure 2.6*D*).

PHYSIOLOGY, ADVERSE EFFECTS, AND MANAGEMENT

Auto-PEEP arises when there is insufficient time for full expiration such that the lungs do not return to their baseline FRC by the start of the next breath. This leads to stacking of the new breath before full expiration of the prior breath and results in a new, increased FRC (see Figures 2.6 and 2.7). This process of stacking continues until the patient's FRC reaches a new equilibrium. This stacking is also referred to as *dynamic hyperinflation*. High levels of auto-PEEP and dynamic hyperinflation can cause several problems. First, in patients intubated for asthma, the increased risk of *barotrauma* at high levels of auto-PEEP correlates best with the degree of dynamic hyperinflation. In addition, auto-PEEP may cause *hypotension* and *falls in cardiac output*, especially in hypovolemic patients. These cardiovascular effects arise because auto-PEEP makes the pleural pressure more positive during the respiratory cycle. This, in turn, decreases venous return to the thorax (the "central tourniquet" effect), with the result being decreased cardiac preload (see Chapter 8).

In addition to these hemodynamic effects, auto-PEEP can result in patients struggling to breathe during mechanical ventilation and interfere with weaning. In both instances, the problem arises due to the need for the patient's spontaneous inspiratory efforts to first overcome the extra elastic load caused by the auto-PEEP before being able to trigger the ventilator. If auto-PEEP reaches 15 to 20 cm H_2O or more, overcoming this extra load can result in respiratory muscle fatigue and prolonged ventilatory support.

One can readily suspect when hypotension is due to auto-PEEP if the blood pressure quickly (almost instantaneously) returns to normal when patients are removed from the ventilator temporarily, such as for tracheal suctioning. Transient removal from the ventilator allows patients with auto-PEEP enough time to empty their lungs. Management of auto-PEEP and its adverse effects are described in Box 2.2.

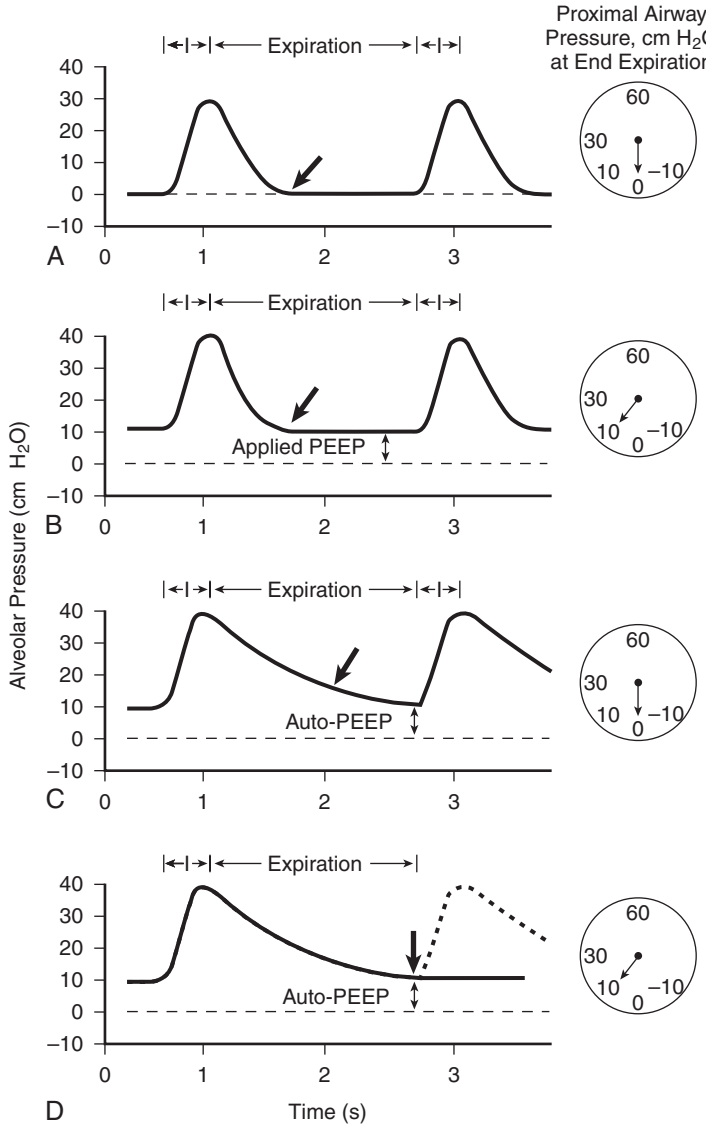


Figure 2.6 Schematic Alveolar Pressures during Ventilation in A/C Mode (without triggering by patient). **A,** No applied PEEP and no auto-PEEP. Note that alveolar pressure returns to baseline (dashed line representing alveolar pressure = 0) well before start of next breath *(arrow)*. **B,** 10 cm H_2O of applied PEEP with no auto-PEEP. Again, note return of pressure to a new baseline (representing alveolar pressure = 10) *(arrow)*. **C,** No applied PEEP with 10 cm H_2O of auto-PEEP. Note the delay in return of the alveolar pressure to baseline (dashed line representing alveolar pressure = 0) *(arrow)* and that the pressure gauge of the ventilator (representing proximal airway pressure at end expiration) does not detect the auto-PEEP. **D,** If one stops expiratory flow just prior to the start of next breath *(arrow)*, the pressure gauge indicates the presence of auto-PEEP and estimates its magnitude. I, inspiration; PEEP, positive end-expiratory pressure. *(Modified from Lanken PN: Mechanical ventilation. In Fishman AP [ed]: Pulmonary Diseases and Disorders, 2nd ed. New York: McGraw-Hill, 1988.)*

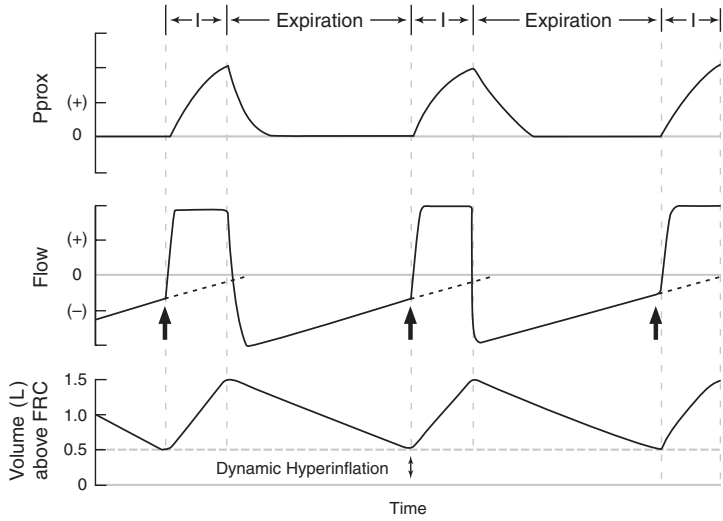


Figure 2.7 Schematic diagram of mechanical ventilation on assist/control mode (with no spontaneous breathing efforts), as in Figure 2.4*A*, but with airway obstruction and auto-PEEP. Note that the expiratory flow does not reach zero before the onset of the next breath *(arrow)*, resulting in dynamic hyperinflation. Delaying the start of the next breath until expiratory flow *(dashed line)* reaches zero would prevent auto-PEEP. PEEP, positive end-expiratory pressure; FRC, functional residual capacity; Pprox, pressure at proximal end of endotracheal tube; I, inspiration; (+), inspiratory flow; (–), expiratory flow.

BOX 2.2 ■ Managing Auto-PEEP

Address Causes of Auto-PEEP

Treat underlying bronchospasm and airway inflammation (see Chapters 75 and 76)
Prolong expiratory time relative to inspiratory time
- Shorten inspiratory time
  - Increase inspiratory flow rate
  - Decrease tidal volume
- Decrease respiratory rate

Change from A/C mode to IMV mode

Address Effects of Auto-PEEP

Expand intravascular volume
Give vasopressors for blood pressure support (if hypotensive)

A/C, assist/control; IMV, intermittent mandatory ventilation; PEEP, positive end-expiratory pressure.

Clinical Pearl

One can determine how much to change minute ventilation to get the desired change in $Paco_2$ by using a graphic approach (see Appendix B, Figure B1) or its algebraic equivalent (Equation 3). This can avoid the common problem of overventilation of chronic CO_2-retaining patients.

$$P_{ACO_2}(1) \times \dot{V}_E(1) = P_{ACO_2}(2) \times \dot{V}_E(2) \qquad \text{(Equation 3)}$$

where $Paco_2(1)$ is the $Paco_2$ with the baseline minute ventilation, $\dot{V}_E(1)$, and $Paco_2(2)$ is the $Paco_2$ predicted to occur after the minute ventilation is changed to another value, $\dot{V}_E(2)$. This

equation assumes that the ratio of dead space to tidal volume (V_D/V_T) and $\dot{V}co_2$ remain constant when minute ventilation is changed. Hence, minute ventilation must be increased or decreased *only by changing respiratory rate*—that is, without changes in tidal volume or ventilatory mode.

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CHAPTER 3

Noninvasive Ventilation

Bernie Sunwoo ■ Richard J. Schwab

Non-invasive ventilation (NIV) refers to the delivery of ventilatory support without the use of an endotracheal or tracheostomy tube. Since the early 2000s, there has been resurgence in the interest and use of NIV in the intensive care unit (ICU). This chapter examines the evolution, indications, contraindications, and practical application of NIV to ensure appropriate and successful use in ICU patients.

The Evolution of NIV

NIV was the mainstay of mechanical ventilatory assistance *outside* the operating suite through to the mid 20th century. Traditionally, it was delivered by *negative pressure* devices such as the "iron lung" that was used predominantly for poliomyelitis patients with respiratory paralysis. When the polio epidemic in Denmark in 1952 created a demand for negative pressure ventilators that overwhelmed the supply of iron lungs, there was a transition to positive pressure mechanical ventilation via translaryngeal cuffed endotracheal tubes. Subsequently, in view of their much higher survival rates, invasive mechanical ventilation became the standard of care for acute respiratory failure (ARF) resulting from polio and other disorders in the ICU.

It was not until the 1980s with the development of nasal masks for continuous positive airway pressure (CPAP), used for the treatment of obstructive sleep apnea (OSA) (Chapter 80), that there was a renewed interest in NIV and specifically non-invasive *positive pressure* ventilation. The positive pressure did not cause the upper airway collapse commonly precipitated by negative pressure ventilators. Soon after, successful NIV use in chronic respiratory failure from a variety of neuromuscular and restrictive thoracic disorders was described.

By preserving the patient's own upper airway defense mechanisms, NIV avoids the potential complications associated with intubation itself, including laryngeal injury. NIV has been shown to lower the risk of nosocomial infections, i.e., ventilator-associated pneumonia (VAP) (Chapter 14); improve comfort and thereby reduce need for sedation; and allow patients to eat, drink, cough, and communicate, permitting greater independence and active patient participation in medical management.

In addition, in selected populations NIV has been shown to be effective in preventing intubation in patients in ARF. This has led to an increase in its use, with a rate of 35% reported among ventilated patients in European ICUs. However, studies have shown large disparities in its utilization among ICUs with apparent underutilization in many centers. One reported reason for the reduced utilization has been lack of physician knowledge and familiarity.

Practical Application of NIV

Understanding the indications and contraindications will identify potential candidates for NIV, but success ultimately depends on proper application. This necessitates knowledge of the available

Additional online-only material indicated by icon.

interfaces, ventilators, and modes of ventilation, and close monitoring in an appropriate setting by an adequately trained multidisciplinary team familiar with its use.

Interface Used in NIV

A proper interface is paramount for NIV to be effective. There are a variety of masks that can be used for NIV. These masks include the oronasal or full-face mask, the nasal mask, nasal "pillows" consisting of soft pledgets inserted directly into the nostrils, mouthpieces held in place by lip seals resembling a snorkel, a total face mask resembling a plastic hockey goalie's mask, and the helmet (fits over the entire head). Interfaces are available in multiple sizes and shapes with various modifications ranging from straps to custom-molded masks to optimize fit and comfort.

Each interface has its own potential advantages and disadvantages, and the choice depends ultimately on the patient. There are no data comparing the effectiveness of the different masks used for NIV. Some degree of air leak either through the mouth or around the mask is universal, and patient cooperation is needed to minimize leak. The full-face mask is often preferred when initiating NIV in patients with ARF in the ICU because these patients tend to mouth breathe. However, the full-face mask interferes with speech, expectoration, and eating and it carries the risks of claustrophobia, aspiration, and rebreathing when compared to the nasal mask. Dentures should be left in place to optimize the fitting of the mask. The nasal mask requires patent nasal passages and mouth closure to minimize air leaks. Heated humidification may minimize mouth leak and improve comfort. Humidification is usually required to prevent upper airway drying. Regardless of the interface chosen, adequate time should be spent with the patient to ensure proper fit, comfort, and acclimatization with appropriate coaching and encouragement.

VENTILATORS

Most NIV ventilators are now positive pressure devices, assisting ventilation by the delivery of pressurized gas to increase transpulmonary pressures and inflate the lungs. Positive pressure devices consist of the standard critical care ventilators designed for use on intubated ICU patients and portable ventilators designed specifically for non-invasive ventilation. Although traditionally these two devices varied in the features offered, the distinction between the two has blurred. Conventional ICU ventilators typically offer better alarm features, allow precise O_2 concentration delivery, minimize rebreathing by having separate inspiratory and expiratory tubing, and are able to generate higher inspiratory pressures compared to portable ventilators. In contrast, portable devices are designed to be more compact, convenient, and economical, with better leak compensation and greater comfort by adjusting triggering, cycling, and inspiratory flow rise times at the expense of limited pressure-generating capabilities, often with peak pressures of 20 to 30 cm H_2O. Rebreathing from the single tubing can be minimized by an expiratory valve but may increase expiratory resistance and work of breathing. In practice, the choice of ventilator used is largely influenced by local availability, expertise, and costs.

VENTILATOR MODES AND SETTINGS

The same modes of ventilation are available for non-invasive ventilation as they are for invasive ventilation and can be divided into volume-cycled and pressure-cycled types. Studies directly comparing the two have suggested better patient tolerance with similar rates of efficacy with pressure-cycled modes. Most randomized controlled trials on NIV in ARF have used pressure-cycled modes and in practice, NIV is largely delivered by pressure-cycled ventilation.

Portable ventilators are designed to deliver continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BIPAP) with or without a backup rate (note that the similar

abbreviation, BiPAP, is a registered trademark of the Respironics Corporation). CPAP delivers a constant set pressure during both inspiration and expiration to increase functional residual capacity and improve oxygenation, but it is strictly not a form of ventilatory assistance. BIPAP provides positive airway pressure in a biphasic manner. An inspiratory positive airway pressure (IPAP) is set for inspiration and a lower expiratory positive airway pressure (EPAP) is set for expiration, whereas the difference between IPAP and EPAP accounts for the degree of ventilator assistance. EPAP not only ensures flow to flush CO_2 from the single ventilator tube and avoid rebreathing, but it increases functional residual capacity, stents open the upper airway to prevent apneas and hypopneas, and counterbalances intrinsic positive end-expiratory pressure (PEEP) in patients with chronic obstructive pulmonary disease (COPD). As with the standard ICU ventilator, the patient triggers it and tidal volumes can vary. A backup rate can be set (spontaneous/timed [S/T], similar to intermittent mandatory ventilation [IMV] [see Chapter 2]). It is recommended if there is any doubt regarding whether the patient will maintain spontaneous respiratory efforts (e.g., during sleep or with sedation for procedures).

Conventional ICU ventilators, like the Puritan Bennett 840 ventilator, offer a non-invasive mode similar to BIPAP, but care must be taken with nomenclature. A pressure support mode of ventilation (PSV) is chosen where a preset level of inspiratory assistance, the pressure support (PS), is delivered (i.e., added to—pressure-wise) to a preset expiratory pressure, the PEEP, when triggered by the patient. A PS of 7 cm H_2O and PEEP of 5 cm H_2O on the standard ICU ventilator is equivalent to an IPAP of 12 cm H_2O and an EPAP of 5 cm H_2O on portable BIPAP devices where PEEP is interchangeable with CPAP.

In some patients, volume-cycled modes of ventilation may be more appropriate, and clinicians should be familiar with its use. This is particularly true when higher airway pressures are required to overcome increased respiratory impedance, as in obesity hypoventilation syndrome (Chapter 80). Generally, higher initial tidal volumes of 10 to 15 mL/kg predicted body weight are needed in these patients to normalize the arterial PCO_2. More recently, there has been interest in proportional assist ventilation, whereby the ventilator applies assistance in proportion to the patient's inspiratory effort in an attempt to optimize patient-ventilator synchrony (Chapter 2).

The mode of ventilation determines the parameters that need to be set, but there is a lack of evidence and no standard guidelines for initial ventilator settings. Goals of care differ in acute and chronic respiratory failure. Prompt correction of ventilation is desired in ARF, but it is generally recommended to start with low pressure settings and titrate up slowly to allow the patient to acclimate to NIV. For example, initial settings could be an IPAP of 8 cm H_2O and an EPAP of 4 cm H_2O, with a backup rate of 10-12 breaths per minute. Furthermore, unlike invasive mechanical ventilation, NIV does not need to be applied continuously to be effective, although in the acute setting, most favor continued use until clinical improvement has been demonstrated. In any case, close monitoring by means of an arterial line to follow arterial blood gases and titration are required.

MONITORING

Initiation of NIV in ARF requires close monitoring by appropriately skilled staff. The site of initiation must be properly chosen. NIV offers the unique opportunity to be provided outside the ICU setting such as in the emergency department, but there needs to be adequately staffed and trained personnel in order to do this successfully. In acute respiratory failure where there is high risk of clinical deterioration requiring endotracheal intubation, NIV must be performed in an ICU environment. A multidisciplinary team involving the physician, nurse, respiratory therapist, and the patient is recommended. Ideally protocol and guidelines should be in place with regular audits to ensure quality control.

Both subjective and objective physiologic responses should be monitored, especially in the initial 2 hours, as prompt improvement has been associated with NIV success. Patients should

be assessed clinically for improvements in respiratory distress, including the use of accessory muscles, tachypnea, chest wall movement, fatigue and level of consciousness, comfort, and patient ventilator synchrony. Vital signs including heart rate and respiratory rate should be monitored, and continuous pulse oximetry should be applied. Frequent arterial blood gases (via an arterial catheter) are recommended as early improvement in gas exchange is predictive of NIV success. The minute ventilation should be adjusted to improve arterial pH and $PaCO_2$. Ideally ventilators able to monitor airway pressures, expired volumes, and airflow should be utilized. Patient tolerance and comfort should be continuously monitored, and this requires close communication with the patient. Close ICU monitoring should mean intubation is not delayed when necessary. If after 2 hours NIV is not successful, conventional intubation should be considered.

Appropriate Patient Selection

NIV has been shown in *selected* categories of patients to decrease mortality, decrease intubation rates, improve gas exchange, reduce dyspnea and work of breathing, decrease complications related largely to being less invasive, decrease length of ICU and hospital stay, and possibly decrease costs. Thus, successful use of NIV in the ICU depends on appropriate patient selection. This involves identifying patients in need of ventilator assistance and understanding both the indications and contraindications for NIV. NIV is not appropriate for all patients. Several studies have also tried to determine predictors of success.

INDICATIONS

The etiology of ARF and its potential reversibility remain key in determining the success of NIV. Strong evidence now supports the use of NIV for acute exacerbations of chronic obstructive pulmonary disease (COPD), acute cardiogenic pulmonary edema, to facilitate extubation in COPD patients, and in immunocompromised patients. (Box 3.1 presents a list of common indications.) NIV should be considered in *all* patients in ARF where mechanical ventilation is considered. NIV should be used as a respiratory assist device to decrease the need for intubation.

BOX 3.1 ■ Indications for Non-Invasive Ventilation in Acute Respiratory Failure

Strong Supportive Evidence

Acute exacerbation of chronic obstructive pulmonary disease (COPD)
Cardiogenic pulmonary edema
Facilitate weaning and extubation in COPD patients
Immunocompromised patients

Favorable Evidence

Postoperative use
Severe asthma exacerbations
Obesity hypoventilation syndrome
Facilitation of high-risk bronchoscopy
Others: pre-intubation oxygenation, chest trauma, cystic fibrosis

Conflicting Evidence

Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS)
Pneumonia
Prevention of postextubation respiratory failure in high-risk patients

Just as essential for successful NIV use is an understanding of the contraindications for NIV. Most of the described contraindications are simply derived from the exclusion criteria of studies examining NIV. NIV should be avoided in hemodynamically unstable patients, patients at high risk of aspiration, and patients unlikely to tolerate a mask interface. Decreased mental status is not per se a contraindication to NIV, but a patient's inability to protect his or her airway (regardless of mental status) is a contraindication. It is not a substitute for endotracheal intubation when needed. Box 3.2 provides a list of contraindications for NIV.

PREDICTORS OF SUCCESS

Despite identifying indications and contraindications for NIV in ARF, failure rates between 4% and 42% have been reported, and clinicians generally are poor in predicting who will do well or fail on NIV. The etiology of ARF remains key as outlined earlier. Patients with hypercapnic ARF are likely to respond to NIV. Multiple studies have attempted to identify predictors of NIV success, most focusing on hypercapnic respiratory failure secondary to COPD. Timely application of NIV appears critical in these patients with higher failure rates in both patients with mild COPD and with advanced hypercapnia and acidemia with impaired consciousness. Rapid early improvement in gas exchange—demonstrated by improved pH and $PaCO_2$, respiratory rate, and heart rate within the first 1 to 2 hours—has been identified as highly predictive of success. Other predictors of success have included lower acuity of illness, younger age, unimpaired level of consciousness and improving encephalopathy, patient ventilator synchrony, less air leak, and the presence of teeth. However, these remain merely population-derived predictors, and clinical judgment and experience remain essential to successfully manage acutely ill individual patients with NIV.

Complications

NIV is generally safe and well tolerated. Complications are usually mild and related to poor interface and air leaks. These include local skin erythema and pressure sores (especially at the bridge of the nose), nasal pain and congestion, sinus or ear pressure, eye irritation caused by air leaks,

BOX 3.2 ■ Contraindications for Non-Invasive Ventilation in Acute Respiratory Failure

Cardiac or respiratory arrest
Inability to protect the upper airway
Inability to cooperate
Inability to clear respiratory secretions, including excessive secretions
Severe hemodynamic instability including cardiac ischemia
Multiorgan failure
Facial trauma, surgery, or deformity
Upper airway obstruction (e.g., due to a foreign body)
Severe upper gastrointestinal bleed
Vomiting
Postoperative surgery that opened upper gastrointestinal organs, such as esophagus, stomach, and duodenum

Modified from American Thoracic Society. International Consensus Conferences in Intensive Care Medicine: Noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 163:283-291, 2001.

Well-Established Indications

Most evidence supporting NIV in acute respiratory failure has been for acute exacerbations of COPD and acute cardiogenic pulmonary edema. There has been a succession of randomized controlled trials, meta-analyses, and systematic reviews supporting the use of NIV in acute hypercapnic respiratory failure caused by acute exacerbations of COPD. NIV has been shown to reduce mortality, reduce intubation rates, reduce ICU and hospital length of stay, improve blood gas abnormalities, and improve vital signs and dyspnea. It is important to recognize most studies included a carefully selected group, and failure rates varying from 5% to 40% have been reported. Studies have demonstrated greater benefit in more severe exacerbations than mild (pH > 7.35), but most generally excluded patients with severe acidemia with hypercapnia (pH < 7.25). Observational studies have described successful use in hypercapnic encephalopathy. NIV is established as standard therapy for selected "stable" patients with ARF resulting from acute exacerbation of COPD. NIV has also been shown to increase weaning rates and decrease duration of intubation with its associated benefits in patients intubated for hypercapnic respiratory failure resulting from acute exacerbations of COPD. In addition NIV can be used as a means of facilitating weaning and extubation in those who fail spontaneous breathing trials.

NIV is also well established in the management of acute cardiogenic pulmonary edema (Chapter 52). Both CPAP and NIV have been shown to decrease the need for intubation, improve respiratory parameters, and improve gas exchange and symptoms in this class of patients. Nonetheless, studies for NIV on mortality have been mixed. By elevating intrathoracic pressure, CPAP is thought to increase functional residual capacity, improve oxygenation, decrease left ventricular preload and afterload, and reduce the work of breathing. CPAP is considered first line by the British Thoracic Society with NIV reserved for patients in whom CPAP is unsuccessful. NIV was categorized as class IIa evidence for the treatment of acute heart failure in guidelines published by the European Society of Cardiology (in which a "class II" designation indicates that there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of a given treatment or procedure and in which a "class IIa" designation indicates that the weight of evidence/opinion is in favor of usefulness/efficacy).

Finally, clinical studies now support the use of NIV in immunocompromised patients. By preserving the patients' own upper airway defense mechanisms, NIV is appealing in this population susceptible to infections, including VAP. NIV has again been shown to reduce intubation rates and to decrease ICU length of stay and ICU mortality in a range of immunocompromised states including AIDS, hematologic malignancies, and following both solid-organ and bone marrow transplantation including lung transplantation. NIV should be used early in immunocompromised patients who begin to manifest signs of respiratory failure.

Potential Indications

There has been growing interest in expanding the role of NIV to other causes of ARF. Acute hypoxemic respiratory failure can be caused by a wide variety of disorders ranging from acute cardiogenic pulmonary edema to acute respiratory distress syndrome (ARDS). This heterogeneous population has made it difficult to reach any definitive conclusions for this population as a group. Although more recent studies have been more promising than earlier studies suggesting poor outcomes in the absence of hypercapnia, as a group the evidence for NIV remains conflicting and in need of better designed studies. Furthermore, studies have largely involved a very select population and highly experienced staff and centers, making any generalizations difficult.

Certain subgroups of hypoxemic respiratory failure appear to do better than others with NIV. Studies examining NIV in community-acquired pneumonia (CAP) have been inconsistent but when compared to other etiologies of ARF have been less encouraging, with failure rates of up to 66% reported. CAP patients with underlying COPD seem to do better, but certainly the evidence

remains inadequate to recommend routine use. Similarly, there is lack of adequately powered randomized controlled trials to recommend routine use of NIV in ARDS.

In acute asthma (Chapter 75), mechanical ventilation is often challenging, but evidence supporting the use of NIV in status asthmaticus has been limited to cohort studies and a prospective randomized pilot study by Soroksky et al. in 2003. NIV has been shown to reduce the need for intubation, improve gas exchange, lower the respiratory rate, improve dyspnea, and reduce need for hospitalization in a carefully selected group. Further large, well-designed studies are needed before any firm conclusions can be made.

Respiratory insufficiency is not uncommon following surgery, and successful NIV use has been described postoperatively, not only in the treatment of postoperative respiratory failure but prophylactically in patients thought to be at high risk of pulmonary complications. Studies have demonstrated improved gas exchange and pulmonary function in a variety of surgeries, ranging from coronary artery bypass grafting (CABG) to some types of abdominal surgery and lung resection. Similarly, some studies have shown favorable prophylactic early use of NIV in selected patients at high risk of postextubation respiratory failure to prevent reintubation in a controlled setting, whereas others have suggested that use of NIV in this setting may only delay and not prevent reintubation while increasing the risk of VAP.

ICUs in the United States have seen an increasingly obese population susceptible to OSA and obesity hypoventilation syndrome (OHS), where patients can present with decompensated hypercapnic respiratory failure. OHS is characterized by obesity and hypoventilation with awake daytime and progressive nighttime hypercapnia in the absence of other causes of hypercapnia. In the ICU setting, NIV is recommended as first-line therapy for patients with OHS in decompensated hypercapnic respiratory failure (see Chapter 80). Typically an arterial line is needed and arterial blood gases should be followed at every 2 to 3 hours while the patient is asleep and less frequently while awake to determine NIV settings.

The role of NIV in patients declining intubation or as a palliative measure is also emerging as an issue in ICUs. Successful use of NIV has been described in the "do not intubate" population to reduce dyspnea where the goal of care is comfort (see Chapter 102). Clear communication with the patient and family remains central in identifying the goals of care and determining the potential role of NIV in this population. It is imperative that a decision regarding endotracheal intubation if NIV fails should be made prior to the initiation of NIV. Otherwise, use of NIV may only prolong the dying process when the latter is not the patient's desired goal of care.

Progressively novel applications of NIV are being utilized in the ICU. NIV has been described during preoxygenation, in patients with chest trauma not requiring immediate intubation, with heliox (helium-oxygen mixtures) in acute exacerbations of COPD, and in patients with cystic fibrosis as a potential bridge to transplantation. In patients with a compromised respiratory status where fiberoptic bronchoscopy can be challenging, NIV has been used successfully during bronchoscopy and should be considered when equipment and skilled staff are available. Similarly, NIV has allowed placement of percutaneous gastrostomy tubes in patients with neuromuscular disease and respiratory insufficiency at risk of deterioration with the sedation required. Finally, although research has focused on the use of NIV for ARF, its role in chronic respiratory failure has long been recognized, and its use in acute-on-chronic hypercapnic respiratory failure as a result of neuromuscular disease or restrictive thoracic disorders deserves mention (see Box 3.2).

and claustrophobia. Artificial skin, refitting or alternative masks, nasal decongestants, heated humidifiers, and nasal emollients may help. Gastric insufflation has been reported in up to 50% but is generally well tolerated, whereas aspiration pneumonia has been reported in 5%. Routine nasogastric or orogastric tubes are not recommended but can be used if necessary. As with invasive mechanical ventilation, there is a potential risk of barotrauma and hemodynamic instability depending on the patients' underlying cardiac systolic function and volume status, but it is likely lower because of lower inflation pressures than conventional positive pressure ventilation. Finally, initial concerns of increased acute myocardial infarction rates with the use of NIV in patients with acute cardiogenic pulmonary edema have not been confirmed.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 4

Liberation and Weaning from Mechanical Ventilation and Extubation

Kristin Hudock ■ Paul N. Lanken

Critical care clinicians routinely "liberate" their patients from mechanical ventilation to allow them to resume breathing on their own. Although the transition from assisted to spontaneous ventilation traditionally has been referred to as "weaning," the process does not have to be gradual or time-consuming. Patients can be classified into simple, difficult, and prolonged weaning categories based on the time they require to wean. Successful weaning is reported over a relatively short period for ~55% of patients (i.e., the simple weaning group), with a minority of patients requiring weeks or more to wean. This chapter addresses two basic questions: (1) When should mechanical ventilation be stopped and the patient extubated? (2) What strategy should be used to liberate a patient from mechanical ventilation?

Ideally, mechanical ventilation should be stopped as soon as the patient can breathe spontaneously and protect his or her airway. To determine this point, several critical tasks should be performed:

1. Ascertain the patient's baseline health and respiratory status, i.e., before the development of acute respiratory failure, by obtaining a thorough medical history from the patient or the patient's family.
2. Determine why mechanical ventilation was first initiated, appreciating both the mechanism and pathophysiology of the patient's respiratory failure (see Chapter 1).
3. Determine the progress the patient has made toward recovery.
4. Assess the patient's ability to maintain adequate oxygenation, ventilation, and airway protection.

The best strategy for successful discontinuation of mechanical ventilation should be the safest and fastest available approach, considering patient-specific factors. The pros and cons of the methods used to discontinue mechanical ventilation, as well as their relative safety and efficacies—based on experience and controlled clinical trials—are discussed here.

When to Stop Mechanical Ventilation: The "First Fix What's Broken" Approach

In this approach, one starts with the underlying assumption that patients cannot be successfully removed from mechanical ventilation unless the problems causing their respiratory failure in the first place are treated and reversed. To accomplish this, one should begin by identifying how the patient's respiratory failure developed (see Chapter 1). Failure of nonrespiratory organ systems that

Additional online-only material indicated by icon.

TABLE 4.1 ■ **Factors and Causes Increasing Ventilatory Demand**

Factors	Causes
Increased V_D/V_T	Acute respiratory distress syndrome, asthma, emphysema, pulmonary emboli
Increased oxygen consumption	Fever, increased work of breathing, morbid obesity, sepsis, shivering, trauma
Increased respiratory quotient (increased CO_2 production relative to O_2 consumption)	Excessive carbohydrate feeding
Decreased set point for $PaCO_2$	Anxiety, central neurogenic hyperventilation, hepatic failure, hypoxemia, metabolic acidosis, renal failure, sepsis

V_D/V_T, dead space-to-tidal volume ratio.
From Lanken PN: Respiratory failure: an overview. In Carlson RW, Geheb MA (eds): Principles and Practice of Medical Intensive Care. Philadelphia: WB Saunders, 1993, pp 754-763.

contributed to the need for mechanical ventilation (e.g., cardiac arrest resulting from a primary cardiac arrhythmia) also need to be addressed appropriately before mechanical ventilation is stopped.

Using a systematic approach (identify both the initial and ongoing disease processes that contribute to a patient's need for mechanical ventilation) can provide clarity in complex patients. For example, a patient being mechanically ventilated immediately after undergoing heart surgery may have a depressed central nervous system (CNS) drive to breathe because of the effects of intraoperative opioids. Moreover, the function of the patient's chest bellows may be compromised by restriction from the operative incision and associated pain as well as by pleural effusions, or by phrenic nerve dysfunction secondary to cold cardioplegia or direct nerve injury. Furthermore, both the mechanics and gas exchange could additionally be affected by the presence of an underlying baseline lung disease—such as chronic obstructive pulmonary disease (COPD)—as well as by acute processes, including atelectasis and pulmonary edema. Finally, the same patient may also have increased CO_2 production because of shivering as a result of hypothermia after cardiac bypass surgery. Collectively, these factors may increase the respiratory effort and, in turn, the work of breathing (WOB) that is required to maintain adequate oxygenation and ventilation.

In the aforementioned example, the workload required by the patient's respiratory pump (also referred to as the ventilatory demand) is increased by the presence of (1) an increased ratio of dead space to tidal volume (V_D/V_T), (2) airflow obstruction, (3) pulmonary edema, (4) atelectasis, and (5) increased CO_2 production (from shivering) (Table 4.1). At the same time, the ventilatory pump capacity may be limited by the surgical incision and pain, loss of lung volumes from multiple causes, respiratory muscle dysfunction caused by phrenic nerve injury, poor diaphragmatic perfusion, electrolyte disorders, and residual effects of neuromuscular blockers (Table 4.2).

Categories of Problems to Consider and Fix

NEUROLOGIC IMPAIRMENT AND CENTRAL NERVOUS SYSTEM DRIVE PROBLEMS

Three categories of neurologic impairment may prevent or delay discontinuation of mechanical ventilation and successful extubation:

1. Loss of upper airway protective reflexes
2. Decreased level of consciousness
3. Effects on the central respiratory drive by hypoventilation syndromes or metabolic acid-base disturbances

TABLE 4.2 ■ **Factors and Examples Reducing Ventilatory Capacity**

Categories and Factors	Examples
Decreased Respiratory Muscle Strength	
Fatigue of respiratory muscle	During recovery period from fatigue, high respiratory rates, increased inspiratory time
Disuse atrophy	Prolonged mechanical ventilation; phrenic nerve injury or transection
Malnutrition	Protein-calorie starvation
Electrolyte abnormalities	Low phosphate, low potassium
Alteration in force-length relationship of the hemidiaphragms	Flattened domes of diaphragms caused by dynamic hyperinflation
Drug-induced weakness	Effects of neuromuscular blocking drugs
Increased Muscular Energetics or Decreased Substrate Supply	
High elastic work of breathing	Low lung or chest wall compliance, high respiratory rates
High resistive work of breathing	Expiratory airways obstruction, high flow rates
Decreased perfusion of diaphragm	Circulatory shock states, anemia
Abnormal Respiratory Mechanics	
Flow limitation	Bronchospasm, upper airway obstruction, airways secretions
Loss of lung volume	Atelectasis, lung resection, pleural effusions
Other restrictive defects	Incisional or other pain-limiting inspiration; tense abdomen caused by ileus, peritoneal dialysis, or ascites, especially intra-abdominal hypertension

Adapted from Lanken PN: Respiratory failure: an overview. In Carlson RW, Geheb MA (eds): Principles and Practice of Medical Intensive Care. Philadelphia: WB Saunders, 1993, pp 754-763.

TABLE 4.3 ■ **Criteria for Adequate Protection of Upper Airway***

1. **Cough reflex:** Present and judged at least moderate in strength
2. **Volitional coughing:** Patient can cough on command with good strength
3. **Tracheal secretions:** Not voluminous, not tenacious, not requiring suctioning at hourly intervals or less, and mobilizable by the patient's efforts
4. **Gag reflex:** Present and at least moderate in strength

*Criteria 1 through 3 must be met before extubation. If only criterion 4 is not fulfilled, the patient can be extubated except if there is a high risk of massive aspiration, such as with partial small bowel obstruction. In all cases, swallowing function after extubation must be carefully tested before any oral intake (see Chapter 22).

Loss of Upper Airway Protection

After extubation, some patients may be at risk of clinically significant aspiration or failure to clear their respiratory secretions. Both can prevent patients from being able to safely maintain spontaneous, independent breathing. Before extubation, patients should be assessed for the presence of adequate cough and gag reflexes and their ability to cough well enough to clear their secretions (Table 4.3). Although unsettled, there are data that some patients without a gag reflex can still be successfully extubated. If patients lack a good cough, however, and are unable to clear secretions by themselves, weaning can continue but extubation should be delayed. If, with repeated testing over several days, the patient cannot adequately protect the airway or clear tracheal secretions, the patient should get an elective tracheostomy. This allows a secure access to the airways for

suctioning secretions and is more comfortable than continuation of an endotracheal (ET) tube. A tracheostomy is also useful for monitoring aspiration of oral fluids during assessment of swallowing function and usually enhances the patient's ability to communicate (Chapter 22).

The presence of swallowing dysfunction should be assessed in all recently extubated patients before oral intake. This is especially important in patients with poor or absent gag reflexes, patients with tracheostomies, or those with a history of suspected aspiration events (Chapter 22).

Decreased Mental Status

Intensive care unit (ICU) patients commonly have a decreased level of consciousness, often because they are sedated with medications. Level of consciousness influences attempts at weaning and extubation in two ways. First, a depressed mental status may result in loss of upper airway protection, as discussed earlier. Second, patients with decreased mental status may also have a decreased respiratory drive. As long as respiratory drive is considerably impaired, assisted ventilation is necessary. However, when the lack of respiratory drive is due to the absence of chemical stimuli to breathe (i.e., a low $PaCO_2$ with high pH), a tapering of assistance in breathing is reasonable and often effective. For example, well-oxygenated patients who are alkalemic because of iatrogenic hyperventilation while on mechanical ventilation may not breathe until their $PaCO_2$ levels are allowed to return to normal.

Several pivotal trials have demonstrated that strategies that minimize sedation can positively influence key patient outcomes, including ventilator weaning. Daily interruption of sedation—with sedatives held in mechanically ventilated patients until they are wakeful—has been found to reduce the average number of days patients spend requiring assisted ventilation. Additional approaches to minimize sedation, including the use of shorter-acting agents or administration of sedative medications in bolus form, especially if done according to a goal directed sedation protocol (carried out by the ICU nursing staff) as opposed to continuous intravenous (IV) infusions, have also been shown beneficial in weaning (Chapter 5). Furthermore, combining the practice of daily sedation interruptions with spontaneous breathing trials (SBTs) resulted in a greater number of ventilator-free days in mechanically ventilated medical patients in a multicenter trial in the United States. Interruption of sedation, however, may increase the risk of self-extubation, and patients should be closely monitored as they resume consciousness.

In addition to medication-induced alterations in consciousness, it is important to assess for hypoventilation resulting from central sleep apnea (CSA), as this may also compromise weaning. CSA occurs as a result of impaired sensitivity to $PaCO_2$ or Pao_2 levels and can manifest in several ways, including as obesity hypoventilation syndrome (see Chapter 80) or periodic breathing (Cheyne-Stokes breathing). This is particularly problematic for patients ventilated with weaning modes that require them to initiate breaths. Patients with CSA may not respond to increasing hypercapnia with the expected elevation in respiratory rate or tidal volume. Moreover, these patients may appear comfortable during a weaning trial, despite an increased $PaCO_2$ level, which is only detected by measuring arterial or central venous blood gases. *Not considering hypoventilation syndromes in the differential for difficult weaning may make patients seem unweanable when, in fact, they only require scheduled ventilatory support at night and with naps* (Chapter 25).

In contrast to patients with hypoventilatory syndromes who do not breathe enough, some patients breathe too much. This includes some patients with brain stem strokes who present with marked tachypnea as a result of central neurogenic hyperventilation. This is challenging because, in general, adults cannot sustain persistent respiratory rates of more than 36 to 40 breaths per minute for too long before they develop respiratory muscle fatigue. Suppression of respiratory drive by high-dose opioids may be successful in such patients, allowing them to be weaned.

Metabolic Acid-Base Disorders

In addition to alterations in ventilation secondary to sedation or CSA, the CNS control of respiratory drive is also affected by both metabolic acidoses and alkaloses. Normally, patients compensate for a metabolic acidosis (serum HCO_3^- <18 to 20 mEq/L) by "blowing down" (compensating) their $PaCO_2$ to maintain their arterial pH in or near the normal range. This respiratory compensation is achieved by hyperventilating, which increases alveolar and minute ventilation (see Chapter 83), but ultimately it may exceed a person's ventilatory capacity and lead to respiratory muscle fatigue. Thus, in addition to correcting the underlying cause of the metabolic acidosis, patients may require bicarbonate supplementation in order for them to wean.

Alternatively, patients with a severe metabolic alkalosis (serum HCO_3^- >45 to 55 mEq/L) may have an elevated arterial pH, which results in a decreased stimulus to breathe, even when their $PaCO_2$ levels increase (Chapter 83). This can promote development of hypercapnia, as respiratory compensation for the metabolic alkalosis. Hypercapnia, in these situations, may be mistakenly attributed to respiratory muscle fatigue, an assumption that can delay weaning.

A related problem occurs in those patients with COPD who have chronic CO_2 retention and develop a compensatory elevated serum bicarbonate level. If their $PaCO_2$ is normalized because of mechanical ventilation, their kidneys no longer need to compensate and their serum bicarbonate level may fall, albeit to a seemingly normal value. Although their arterial blood gas (ABG) may appear "normal," prior to discontinuation of mechanical ventilation, these patients often fail extubation because of increasing respiratory acidosis, which causes dyspnea, tachypnea, and respiratory muscle fatigue. The preferred strategy for patients with COPD who have chronic CO_2 retention is to use ventilator settings that maintain their $PaCO_2$ levels at their baseline elevated values (see Appendix B). This approach also tends to result in sustained elevation of their serum HCO_3^- so that, when the patient's pulmonary function has returned toward its baseline, weaning has a reasonable chance to be successful.

CHEST BELLOWS AND PERIPHERAL NERVOUS SYSTEM PROBLEMS

Respiratory Muscle Weakness

In some patients, respiratory muscle weakness occurs as a primary event (e.g., in some neuromuscular disorders; see Chapter 67). In other patients, decreased respiratory muscle strength may occur secondary to the effects of critical illness or respiratory failure (see Chapter 48 and Table 4.2), such as when fatigued respiratory muscles need additional time to recover (which may take up to 1 day). Moreover, with muscle disuse—as occurs with modes of mechanical support that do not require significant engagement of the patient's respiratory muscles—or protein malnutrition, the muscles atrophy. Indeed, evidence of histologic myofiber atrophy has been demonstrated in the diaphragm of humans mechanically ventilated for less than 1 day, possibly because of altered proteolysis. In response to concerns regarding ICU-acquired weakness, several clinical trials were found that, compared to usual care, daily physical and occupational therapy coupled with sedative interruptions resulted in earlier weaning, as evidenced by a greater number of ventilator-free days and a larger number of patients who regained their baseline functional independence (Chapters 5 and 21) .

Decreased muscle function may also be exacerbated by metabolic disorders such as hypophosphatemia and hypokalemia. Furthermore, severe hyperinflation—from airflow obstruction and auto–positive end-expiratory pressure (auto-PEEP)—compromises the efficiency of the length-tension relationship of the normally situated diaphragm and exacerbates the effects of muscle weakness.

Changes in Chest Bellows Function

Various factors can limit lung or chest expansion. In postoperative states, both the architecture of the incisions as well as the degree of pain may limit expansion. Prior to modern pain management

strategies (see Chapter 87), on the first postoperative day, a patient's vital capacity often decreased to only ~25% of preoperative values after thoracotomy as well as after upper abdominal surgeries (e.g., open cholecystectomy). Other common factors that can alter expansion include the presence of a flail chest (resulting from trauma or closed chest cardiac resuscitation), pleural effusions, major atelectasis as well as abdominal distention (from air, ascites, dialysate, or edema). Similarly, intra-abdominal hypertension and abdominal compartment syndrome (Chapters 90 and 97)—often a result of extensive fluid resuscitation—can limit diaphragmatic excursion, thereby decreasing forced vital capacity (FVC) and increasing dead space ventilation.

AIRWAYS PROBLEMS

Upper Airway Injuries

Both iatrogenic and noniatrogenic injuries can result in upper airway obstruction leading to respiratory failure requiring initiation of mechanical ventilation. Patients who experienced difficult intubations—either for anatomic or situational reasons—may develop temporary vocal cord edema or permanent injury. Likewise, patients who undergo head and neck surgery may suffer from direct vocal cord injury. Smoke inhalation can result in both thermal and chemical injuries to the upper airways, sometimes with delayed manifestations of edema and sloughing that can limit air passage. Additionally, patients who develop angioedema—either secondary to an autoimmune disease or after exposure to medications—need adequate time for swelling to improve before successful extubation can occur.

Respiratory failure can occur from acute upper airway injury because of a resulting decreased ventilatory capacity—from upper airflow obstruction—and a compromised force-tension relationship from hyperinflation (flatting the domes of the diaphragms). In addition, as a rule, ventilatory load is increased by an increased resistive work of breathing and tachypnea.

Depending on the nature of the upper airway injury, it may take several days or more before patients are candidates for successful extubation. During this time, if the patient can tolerate it, he or she should be mechanically ventilated with as little support as is necessary to keep the patient breathing comfortably. Modes of ventilation that require patients to utilize their own respiratory muscles (e.g., pressure support [PS]) are often favored so as to limit muscle disuse atrophy that may occur when patients are ventilated with assist control (AC) modes that provide full support.

Two approaches have been used to determine if upper airway edema has sufficiently improved for successful extubation to occur. The first method involves direct visualization of the upper airway and vocal cords with a bronchoscope or a laryngoscope while the ET tube is in place. However, visualization of the laryngopharynx and vocal cords is often limited by the presence of the ET tube plus a feeding tube. In some cases, patients can also be extubated over a bronchoscope, which may allow a brief additional assessment of vocal cord movement as the ET tube is removed. Extubating a patient for whom one has high concern for upper airway patency should be done in coordination with an anesthesiologist, an otorhinolaryngologist, or both at the bedside.

An alternative approach to assess upper airway patency is to perform an "air leak" test—that is, to measure the air leak produced by deflation of the ET tube cuff—as the patient receives a defined tidal volume (e.g., 500 mL) during volume cycled mechanical ventilation. In patients with high risk for postextubation stridor, if the patient's air leak around the deflated cuff is nil or modest (<100 mL per breath of 500 mL), one can assume that supraglottic obstruction may be present and delay extubation until after treatment of presumed laryngeal edema (i.e., IV dexamethasone and sitting the patient more upright in bed). However, because prospective studies have reported false positives (i.e., patients who had decreased air leaks but were extubated successfully) when applied to general ICU patients, some clinicians elect to limit its use to selected high-risk patients.

Inspiratory Loading as a Result of Auto-PEEP

An increased inspiratory load may also occur as a result of auto-PEEP, also known as intrinsic PEEP or dynamic hyperinflation, resulting from obstructive airways disease (e.g., asthma or COPD [Chapters 75 and 76]). To trigger the ventilator to provide synchronous support, the patient's inspiratory efforts must be detected by the ventilator. This is usually done by setting the ventilator to recognize when the patient generates a specific inspiratory flow (or negative pressure), also known as the triggering threshold. If auto-PEEP is present, however, the patient's inspiratory efforts must generate enough negative intrathoracic pressure to overcome *both* the auto-PEEP and the set threshold to trigger the ventilator (see Chapter 2, Figure 2.7).

If auto-PEEP is high (>12 to 15 cm H_2O), this places a substantial extra burden on the patient's inspiratory muscles and may result in respiratory muscle fatigue. For example, if a patient has 14 cm H_2O of auto-PEEP and a ventilator triggering sensitivity of −1 cm H_2O, the patient must generate 15 cm H_2O of negative intrathoracic pressure for the ventilator to detect the patient's attempt to initiate a breath. Thus, the presence of unappreciated and untreated high auto-PEEP may result in failed weaning attempts.

Auto-PEEP is a common cause of ventilator dyssynchrony. Treatment of auto-PEEP during weaning trials consists of aggressive treatment of the underlying obstructive airways disease (Chapters 75 and 76) as well as maneuvers to increase expiratory times to allow more time for alveolar emptying. If auto-PEEP persists, additional external PEEP may be applied at ~80% of the level of the auto-PEEP present to decrease work of breathing. This external PEEP "resets" the triggering sensitivity level of the ventilator—to overcome the increased positive pressure present at the alveoli (because of auto-PEEP). Most ventilators can measure auto-PEEP by performing an end expiratory pause; however, if the patient is breathing very quickly this maneuver is difficult to do. Alternatively, with some ventilators, one can manually estimate auto-PEEP by occluding the expiratory tubing or port just before the start of the next inspiration and reading the pressure in the circuit on the pressure gauge of the ventilator or the digital readout (see Figure 2.7).

Performing a Tracheostomy to Facilitate Weaning

Traditionally, recommendations for a tracheostomy were commonly made after about 2 weeks of mechanical ventilation (see Chapter 22). The purpose of the tracheostomy was to facilitate weaning and to provide an airway that was more secure and comfortable than the ET tube. Gradually, however, intensivists have adopted the practice of extending the period of use of ET tubes beyond 2 weeks, depending on when they anticipate the patient can be extubated.

Tracheostomy tubes may also facilitate weaning, particularly in patients who require several weeks of mechanical ventilation, because the ET tube is often an unrecognized source of increased work of breathing and auto-PEEP. Moreover, several studies have reported that replacement of an ET tube with a tracheostomy of the *same* internal diameter resulted in significant *decreases* in work of breathing (WOB) and in auto-PEEP. This is related to increased resistance in the tube because of the development of a biofilm (a microlayer of secretions) that lines the interior surface of the ET tube, particularly in patients ventilated for several weeks. The increased WOB due to the biofilm may delay weaning further in patients with compromised pulmonary function. Additionally, the microorganisms that create biofilms can be dislodged into the lower respiratory tract with routine suctioning and may increase the risk of ventilator-associated pneumonia. Based on these two concerns some ICU practitioners favor early tracheostomy in patients who are expected to require several weeks of mechanical ventilation.

ALVEOLAR FLOODING PROBLEMS

Conditions that affect the alveoli—the portion of the lower respiratory tract responsible for gas exchange—often present with (1) a persistent need for high F_{IO_2} (≥0.5) or for PEEP (>5 cm H_2O), (2) a high elastic work of breathing (caused by stiff lungs), and (3) an increased drive to breathe, causing tachypnea (resulting from stimulation of vagal and phrenic afferents). The lung stiffness and the restrictive defect produced by flooding of alveoli with edema fluid also limit ventilatory capacity. Similarly, hypoxia and hypercapnia can also be seen when alveoli are filled with inflammatory exudates (acute respiratory distress syndrome [ARDS] or pneumonia) or blood (in isolated or diffuse hemorrhage).

Even though supplementary high-flow oxygen can be administered after extubation, one should generally only consider patients eligible for discontinuation of mechanical ventilation when they are able to maintain adequate oxygenation without high levels of F_{IO_2} and PEEP (Table 4.4). If mechanisms to maintain normoxemia are borderline before weaning, the risk of hypoxemia increases with weaning and after extubation.

PROBLEMS FROM NONRESPIRATORY ORGAN SYSTEMS

Conditions affecting organs other than the respiratory system can also delay or prevent successful weaning. Cardiac disorders including left ventricular failure with pulmonary edema (often occult or refractory to therapy) may result in alveolar filling problems. Atrial and ventricular arrhythmias as well as episodic or persistent hypotension—often requiring vasopressor therapy—may cause low cardiac output states that result in decreased perfusion to the kidneys or skeletal muscles, including the diaphragm.

Patients who have *renal failure* as well as acute respiratory failure may also be problematic to wean for several reasons. First, they are susceptible to intravascular volume overload, which can result in pulmonary and chest wall edema. Second, renal failure usually results in a metabolic acidosis—and lower serum bicarbonate levels—which leads to increased ventilatory demands in order to provide respiratory compensation. Such a metabolic acidosis is particularly problematic in patients with COPD with chronic CO_2 retention who normally rely on their kidneys to provide metabolic compensation in the form of serum bicarbonate elevation. Even with intensive intermittent hemodialysis, it is often difficult to sustain the serum HCO_3^- at the consistently elevated level necessary to avoid tachypnea and muscle fatigue after extubation in patients with chronic respiratory acidosis. In these situations, supplementation with oral bicarbonate or bicitrate may be appropriate.

TABLE 4.4 ■ **Criteria for Adequate Capacity for Oxygenation***

1. **Ability** to achieve an arterial oxygen saturation ≥ 92–95% or Pa_{O_2} > 60 mm Hg with
   F_{IO_2} ≤ 0.5 and
   PEEP ≤ 5 cm H_2O and
   Pa_{O_2}/F_{IO_2} > 200
2. **Trend** of F_{IO_2} and PEEP in the right direction:
   F_{IO_2} (at present) equal to or lower than the F_{IO_2} used the previous day
   PEEP (at present) equal to or lower than the PEEP used the previous day
3. **Stability** in oxygenation as demonstrated by no episodes of arterial desaturation < 88% in the prior 24 hours

*All three criteria need to be present at the time of assessment.
PEEP, positive end-expiratory pressure; F_{IO_2}, fraction of inspired oxygen.

The presence of *end-stage liver disease* (ESLD) also complicates the process of weaning from mechanical ventilation in multiple ways. Periodic episodes of active gastrointestinal bleeding—because of varices or severe coagulopathy—may require the need for mechanical ventilation to be extended for airway protection (to prevent aspiration of blood). The presence of ascites may limit chest bellow expansion and full descent of the diaphragms, as well as contribute to hepatohydrothorax (pleural effusions), resulting in restrictive defects. Finally, ESLD results in a respiratory alkalosis from hyperventilation, often with a concomitant metabolic acidosis caused by elevated lactate levels, both of which can increase ventilatory load.

WHEN TO STOP ASSISTED VENTILATION: TESTING FOR PHYSIOLOGIC CAPACITIES

To do well after stopping assisted ventilation and extubation, patients need to be able to do the following:

1. Protect and clear their upper airway
2. Maintain adequate oxygenation
3. Sustain sufficient ventilation

Criteria for assessing the adequacy of each these functions are presented in Tables 4.3 to 4.6.

A number of other parameters have traditionally been used to assess whether patients are able to be removed from the ventilator, including a vital capacity > 10 mL/kg predicted body weight (PBW), maximum inspiratory pressure (MIP) (also referred to as negative inspiratory force or NIF) less negative than −20 cm H_2O, resting minute ventilation < 10 L/min, maximum voluntary ventilation (MVV) > 2 times the resting minute ventilation, and V_D/V_T > 0.6. Prospective trials of these parameters, however, indicated that their predictive value as screening tests is poor and that the single screening test with the most utility is the rapid-shallow breathing index (Table 4.5).

Rather than using a single test to determine if a patient is capable of maintaining adequate ventilation, most intensivists also utilize spontaneous breathing trials (SBTs), after patients meet certain screening criteria similar to those listed in Tables 4.4 to 4.6. The steps of this screening process are often written as unit-based protocols that are managed by ICU respiratory care practitioners and nurses. Management of these protocols by persons other than physicians permits screening to be performed on a daily basis routinely before physician rounds. In ICUs that use these protocols in this manner, they have become established as effective tools for timely liberation and extubation. Controlled studies indicate that such protocols lead to shorter periods of

TABLE 4.5 ■ **Assessing Ventilatory Capacity: Screening Criteria**

Patient Must First Pass All Criteria Listed
Absence of serious cardiac arrhythmias
Absence of hemodynamic instability and off vasopressors (except low-dose dopamine)
Presence of respiratory efforts
Oxygenation criteria met (see Table 3.4)
Adequate capacity to cough and clear secretions (see Table 3.3)
Respiratory rate-to-tidal volume ratio < 105 breaths/min/L*

*Perform the test only if all the preceding criteria in the table are met. Test: Allow patient to breathe spontaneously for 1 minute with 5 cm H_2O continuous positive airway pressure, no change in F_{IO_2}, and no mandatory breaths. Use ventilator to measure minute ventilation and respiratory rate (RR) and obtain mean tidal volume (in liters) by dividing the minute ventilation by the rate. Finally, divide the rate by the mean tidal volume to obtain the ratio. (For example, RR = 30, $\dot{V}E$ = 10 L/min, VT = 0.33 L, RR/VT = 30/0.33 = 91.)

TABLE 4.6 ■ **Assessing Ventilatory Capacity: Spontaneous Breathing Trial (SBT)**

1. **Screening criteria:** Patient must have passed all criteria listed in Table 4.5 earlier on same day
2. **Preparatory steps:**
   Place patient as upright as possible in bed
   Reassure patient about breathing on his or her own
   Suction airway well, ensure that monitoring is in place, and note baseline vital signs
   Keep F_{IO_2} the same as on the ventilator or increase current F_{IO_2} by 0.1
   Select one: CPAP with PS = 5 cm H_2O, Flow-Bye mode, or T-piece
3. **Trial of spontaneous breathing***

Plan to allow patient to breathe spontaneously for up to 2 hours

Monitor ECG, pulse, respiratory rate, tidal volumes (if on CPAP or Flow-Bye), Sa_{O_2} by pulse oximetry, blood pressure, and signs of dyspnea or other serious problems (e.g., chest pain consistent with angina)

Stop the trial earlier for any of the following indications:
   Respiratory rate > 35 breaths/min for > 5 min
   Arterial O_2 saturation < 90%
   Heart rate > 140 beats/min or sustained changes > 20% over or under baseline rate
   Serious arrhythmias
   Systolic blood pressure > 180 mm Hg or < 90 mm Hg
   Moderate or severe respiratory distress (increased anxiety or diaphoresis)

4. **Successful trial:** The patient breathes without mechanical ventilation for 2 hours

CPAP, continuous positive airway pressure; ECG, electrocardiogram; PS, pressure support; Sa_{O_2}, oxygen saturation.

**Modified from Ely EW, Baker AM, Dunagan DP, et al: Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med 335:1864-1869, 1996.*

mechanical ventilation and ICU length of stay without an increase in the rate of reintubations compared to usual care not using such protocols.

SUCCESSFUL TRIAL OF SPONTANEOUS BREATHING

Test Characteristics

If a patient meets the screening criteria (see Table 4.5), passes an SBT (Table 4.6), and demonstrates adequate capacity to protect and clear the upper airway (see Table 4.3), then he or she should be considered a good candidate for extubation. To make the final decision regarding stopping ventilation and extubation; however, one should consider the combination of screening criteria and SBT results as one diagnostic "test" having a false-positive rate (the patient passes the test but needs to be reintubated) and false-negative rate (patient fails the test but can ventilate spontaneously successfully). The percentage of extubated patients passing this "test" who require reintubation (i.e., the false-positive rate) varies among studies and centers but has been reported as high as 15% to 20%. In a study of patients comparing extubation successes and failures—all of whom passed an SBT—only increased age and the presence of cardiac or pulmonary disease were more likely in the group that failed extubation. Other variables did not predict who would experience extubation failure. New strategies, such as assessing lung aeration by ultrasound, may better predict those who fail extubation, but further study is needed. Given the sizable reintubation rates and a poor ability to determine who will fail extubation, most patients should remain in the ICU after extubation for close monitoring for 12 to 24 hours. To date, prospective studies have not defined the optimal interval for ICU monitoring following extubation, so this decision should be based on patient-specific risk factors.

Extubation Steps

In general, extubation is carried out through a series of steps: (1) explain to the patient about the extubation, (2) sit the patient erect in bed, (3) suction the airways, (4) suction laryngeal secretions that may have pooled above the cuff, (5) deflate the cuff and remove the artificial airway, (6) treat the patient with an appropriate level of supplemental oxygen (increasing the F_{IO_2} while on the ventilator by 0.1), and (7) monitor vital signs and clinical appearance for signs of distress.

RESPIRATORY FAILURE AFTER EXTUBATION

Postextubation Upper Airway Obstruction

Upper airway obstruction and stridor occur in a small percentage of patients, usually within ~60 minutes of extubation. If this occurs, the patient should be monitored closely for respiratory failure. Treatment includes inhaled alpha-adrenergic agents (to vasoconstrict blood vessels), intravenous (IV) corticosteroids (e.g., 60 mg methylprednisolone), and noninvasive ventilation (NIV) (Chapter 3). If stridor progresses to respiratory failure despite treatment, reintubation is needed. Some patients may be known to be at high risk for upper airway obstruction after extubation (e.g., persons initially intubated for smoke inhalation, stridor, traumatic intubations in the field, or acute epiglottitis). In these cases, it is prudent to check the patency of the supraglottic space surrounding the ET tube before extubation as discussed earlier.

Use of NIV after Extubation

The practice of extubating all patients to NIV has not been demonstrated to reproducibly decrease rates of reintubation. In select groups, particularly difficult-to-wean patients with concomitant chronic hypercapnic respiratory failure, however, extubation to NIV has been shown to be beneficial. Furthermore, use of NIV as a rescue therapy for respiratory distress after extubation is a generally accepted alternative to immediate reintubation in many scenarios.

UNSUCCESSFUL TRIAL OF SPONTANEOUS BREATHING

Failing the Trial

In general, if a patient fails an SBT (see Table 4.6), the patient should not be considered ready for extubation. In certain cases, however, the patient may be unsuccessful in the trial but still may be able to breathe successfully on his or her own (i.e., a false-negative result). Although data are limited, one multicenter weaning trial reported by Girault et al in 2011 found that about 30% of ICU patients did *not* develop recurrent respiratory failure if extubated right after failing their first SBT. In borderline cases, the final decision whether to extubate should be based on both the results of the SBT as well as the overall clinical trajectory of the patient. For patients who fail an SBT and are not thought to be capable of ventilating adequately on their own, most intensivists would begin a trial of weaning. Simultaneously, clinicians should optimize the patient's ventilatory capacity and decrease ventilatory demand by identifying and treating other potentially contributing factors (see Tables 4.1 and 4.2).

Weaning Trials

All weaning techniques are based on the assumption that many patients on mechanical ventilation with poor ventilatory capacity can benefit from "training" their respiratory muscles, much like athletes train to improve their performance. Although this seems reasonable from a physiologic perspective, there have been conflicting data regarding whether it is beneficial in ventilated patients. One trial suggests that inspiratory muscle training may improve outcomes in patients requiring prolonged ventilation, but further studies are needed.

Several controlled clinical trials have studied approaches to weaning mechanical ventilation in those patients who failed their SBT after 1 to 4 weeks of the assist-control mode of mechanical ventilation. These studies found that weaning with once- or twice-daily T-piece trials or with pressure support (PS) resulted in a shorter duration of mechanical ventilation when compared with weaning using synchronized intermittent mandatory ventilation (SIMV).

Despite the results of these studies, some ICUs continue to use intermittent mandatory ventilation (IMV) for weaning based on their personal or institutional experiences. For example, in challenge-to-wean patients—that is, patients with prolonged ventilator dependency (>21 days)—factors other than the specific weaning method used also seem important for successful outcomes. These include providing good nutrition, establishing sleep hygiene, controlling infection, setting goals, and using a multidisciplinary team to provide a program of comprehensive care (see Chapters 25 and 109).

Unassisted Breathing or T-Piece Trials

T-piece trials entail disconnecting the ET tube from the ventilator and allowing patients to breathe through a plastic T-shaped accessory (hence the name T-piece) (Figure 4.E1). Some ventilators also have a special mode, which can substitute for a T-piece trial without losing the ventilator's monitoring capabilities. The patient starts breathing on his or her own, usually for the duration that was tolerated during previous trials of spontaneous breathing, then that duration is gradually increased. If respiratory distress develops before the target time period is finished and the patient cannot be assisted in his or her efforts with coaching (or mild anxiolysis if anxiety is the main problem), then the patient is returned to the ventilator for a rest period. A repeat T-piece trial is usually attempted later that same day, but it may be delayed until the morning of the next day in order to further improve the patient's clinical situation. Tracheostomy collars, instead of T-pieces, are generally used for unassisted weaning trials in patients with tracheostomies.

If the patient breathes well on a T-piece or equivalent for one full 2-hour period, some clinicians would extubate the patient at that point; others would extubate after several such 2-hour periods of successful breathing, especially if the patient had undergone a prolonged course of mechanical ventilation. Because of their abrupt transition from 100% assisted breaths to 100% unassisted breaths, T-piece or similar methods of weaning may not work as well as a weaning method that provides a tapering of support in patients with congestive heart failure. For these patients, the complete loss of positive pressure ventilation when they are removed from the ventilator may exacerbate their congestive heart failure, resulting in dyspnea and respiratory distress. Another effect of abrupt removal of PEEP includes derecruitment and possibly desaturation. Although controversial, some proponents of T-piece trials believe that the resistance of the ET tubing (present in T-piece trials but potentially overcome by use of low pressure support or PEEP approximates the upper airway resistance that is present after extubation because of upper airway inflammation incited by the presence of an ET tube).

Pressure Support Weaning

A commonly used alternative approach to T-piece trials involves use of pressure support, supplied by the ventilator (to overcome airway resistance of the tube), with or without concomitant continuous positive airway pressure (CPAP). The protocol for pressure support weaning (Table 4.7) allows patients to be weaned over the course of 1 day if they prove themselves capable of unassisted breathing. Finishing the weaning trial by 7 or 8 p.m. is important because many ICUs traditionally avoid continuing active weaning and extubation after this time in the evening. This restriction is because traditionally most units have fewer staff members at night to provide close monitoring, but this may change with newer staffing models that incorporate in-house nocturnal intensivist coverage.

Importance of Protocols in Weaning

There is robust evidence that use of a weaning protocol decreases duration of mechanical ventilation. Most successful weaning protocols include objective criteria to assess readiness to wean,

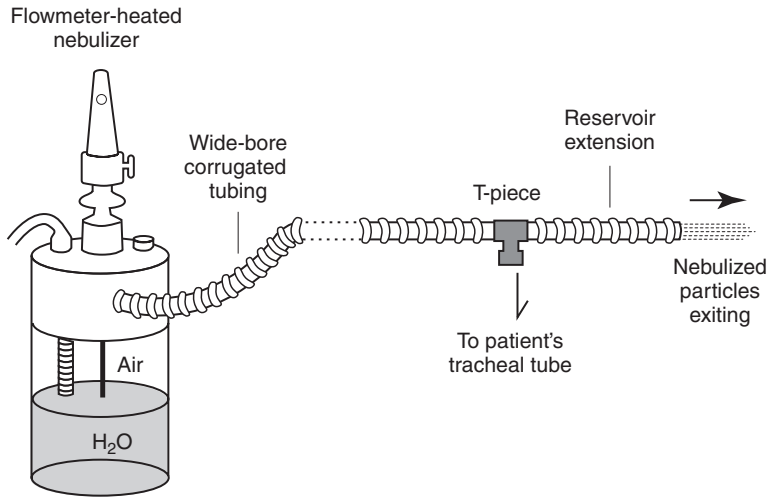


Figure 4.E1 Equipment utilized in a T-piece trial. Oxygen is mixed with entrained ambient air in a heated nebulizer chamber to produce a specific F_{IO_2}. This is then delivered to the patient's tracheal tube via wide-bore tubing and the T-piece. The extension tubing is used to prevent inspiration of ambient air. *(From Lanken PN: Weaning from mechanical ventilation. In Fishman AP [ed]: Update: Pulmonary Diseases and Disorders. New York: McGraw-Hill, 1982.)*

TABLE 4.7 ■ **Pressure Support Weaning Protocol***

1. Place patient on a level of pressure support (PS) to keep the patient's respiratory rate at 25 (or 30†) breaths/min
2. After 120 min at this level of PS with no signs of distress (see Table 4.6) and respiratory rate (RR) ≤ 25 (or ≤ 30) breaths/min, decrease PS by 2–4 cm H_2O. If distress develops or RR > 25 (or > 30) breaths/min, go to step 5
3. After each time period, as in step 2, decrease PS by 2–4 cm H_2O and observe for distress or RR > 25 (or ≤ 30) breaths/min
4. After 120 min at PS of 5 cm H_2O without distress or RR > 25 (or > 30) breaths/min, extubate the patient
5. If distress develops or RR > 25 (or > 30) breaths/min, return to the next higher level. Allow at least 2 hours for recovery to baseline before lowering PS again
6. To promote rest and sleep, return patient to the next higher PS level or to full ventilatory support (PS level used in step 1 or assist-control mode) in the evening and at night

*Patient is assumed to have met all the airway protection criteria in Table 4.3, the oxygenation criteria in Table 4.4, and the nonpulmonary screening criteria listed in Table 4.5. Some patients may need to have a minimum tidal volume or spontaneous minute ventilation or both specified in order to proceed with weaning in addition to described threshold for RR.

†Some protocols use 30 breaths/min as the threshold instead of 25 breaths/min.

Modified from Esteban A, Frutos F, Tobin MJ, et al: A comparison of four methods of weaning patients from mechanical ventilation. N Engl J Med 332:345-350, 1995.

a specific plan for stepwise reduction in ventilator support, and a list of criteria to meet before extubation. These protocols can be administered by respiratory care practitioners and ICU nurses as well as managed by computer-based closed-loop systems.



An annotated bibliography can be found at www.expertconsult.com.

BLOOD GASES IN WEANING AND EXTUBATION

Although measurement of arterial blood gases (ABGs) in mechanically ventilated patients has been the practice of most intensivists and seems clinically reasonable, no recent large trials validate their use in patients who are weaning. There is some evidence, however, that ABGs drawn during SBTs may alter a clinician's decision to extubate, but studies do not recommend the use of ABGs in isolation. In some groups of patients, particularly patients with chronic hypercapnia, an ABG during an SBT may be useful to detect changes in $PaCO_2$ before they become clinically significant or symptomatic.

A related question is whether or not to monitor ABGs in patients after extubation, in order to more rapidly detect those who will fail. Studies examining the routine use of ABGs following extubation in medical ICU patients did not find that ABGs—drawn in the initial hours following extubation—predicted extubation failure any better than routine clinical monitoring in the ICU.

As obtaining an ABG may be painful—and if to be done serially may require an indwelling arterial catheter, which can serve as a nidus for infection or thrombosis—some clinicians favor central venous blood gases (VBGs) (i.e., obtained from a central venous catheter [Chapter 11]). Several small studies have confirmed a good correlation for pH and PCO_2 between venous and arterial blood gases in mechanically ventilated patients in medical ICUs. Formulas have been developed to convert the measured venous pH to a predicted arterial pH value. Additionally, this correlation may be stronger in patients who are hemodynamically stable. However, there are several disadvantages to relying on central VBGs, including (1) loss of the Pao_2, used to determine the severity of hypoxemia (and categorize a patient as ARDS [see Chapter 73]), (2) it is an inexact measurement of acid-base status, and (3) loss of invasive blood pressure monitoring supplied by an indwelling arterial catheter.

Despite these drawbacks, the central VBG does provide information regarding tissue oxygenation in the form of the central venous oxygen saturation ($ScvO_2$)—an estimation of the mixed venous saturation (SvO_2) (see details of its use in severe sepsis in Chapter 10). Small studies suggest that the mixed venous saturation or SvO_2 may be a useful parameter to follow during an SBT as it estimates how a patient's cardiac output and tissue oxygen consumption changes with the stress of weaning, although this measurement requires placement of a pulmonary artery catheter. Data suggest that a drop in the more-practical-to-obtain $ScvO_2$ may predict extubation failure in difficult-to-wean patients. However, these findings need to be confirmed. Although the $ScvO_2$ provides useful information, it may not accurately reflect the SvO_2 in all patients (e.g., because of positioning in the right atrium or venal cavae) and should not completely eliminate the need for ABGs in most patients.

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This meta-analysis reports that use of weaning protocols decreased the duration of mechanical ventilation in a pooled set of trials performed in mixed, neurosurgical, medical, and surgical units.

Brochard L, Rauss A, Benito S, et al: Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med 150:896-903, 1994.

This landmark clinical trial compared weaning methods; it found that pressure support had a shorter weaning duration than T-piece trials or intermittent mandatory ventilation (IMV) (which was the slowest method). The reintubation rate within 48 hours was 7.3%.

Burns KEA, Meade MO, Lessard MR, et al: Wean earlier and automatically with new technology (The WEAN study): A multicentre, pilot randomized controlled trial. Am J Resp Crit Care Med online publication on March 22, 2013.

This is the first published randomized controlled trial to compare an automated weaning system to a standardized, paper-based weaning protocol. In 92 ICU patients receiving mechanical ventilation, those weaned by the Automated Weaning had significantly shorter median times to first spontaneous breathing trial (SBT) (1.0 vs. 4.0 d), extubation (3.0 vs. 4.0 d) and successful extubation (4.0 vs. 5.0 d).

Diehl J, El Atrous S, Touchard D, et al: Effects of tracheotomy on work of breathing. Am J Respir Crit Care Med 159:383-388, 1999.

This study documents decreased work of breathing when endotracheal tubes were replaced by tracheotomy tubes of the same internal diameter.

Ely EW, Baker AM, Dunagan DP, et al: Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med 335:1864-1869, 1996.

This clinical trial established the efficacy of respiratory therapist–driven protocols for trials of spontaneous ventilation. The reintubation rate within 48 hours was 4%.

Esteban A, Frutos F, Tobin MJ, et al: A comparison of four methods of weaning patients from mechanical ventilation. N Engl J Med 332:345-350, 1995.

This is the second landmark clinical trial comparing weaning methods; it found that once or twice daily T-piece trials were superior to pressure support or IMV (which again was the slowest method). The reintubation rate within 48 hours was 17.7%.

Girard TD, Kress JP, Fuchs BD, et al: Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomized controlled trial. Lancet 371:126-134, 2008.

This multicenter trial demonstrated that pairing spontaneous breathing trials (SBTs) with sedation interruptions reduced the number of days that patients needed mechanical ventilation but resulted in higher rates of self-extubation. Coupling these interventions also resulted in a lower risk of death for 1 year.

Girault T, Bubenheim M, Abroug F, et al: Noninvasive ventilation and weaning in patients with chronic hypercapnic respiratory failure. a randomized multicenter trial. Am J Respir Crit Care Med 184:672-679, 2011.

This is a randomized multicenter study investigating the effectiveness of noninvasive ventilation as an early weaning technique in patients with chronic hypercapnic respiratory failure intubated for acute respiratory failure.

Jubran A, Grant BJB, Duffner LA, et al: Effect of pressure support vs unassisted breathing through a tracheostomy collar on weaning duration in patients requiring prolonged mechanical ventilation. A randomized trial. JAMA 309:671-677, 2013.

This randomized controlled trial (RCT) of 316 patients in a single long-term acute care hospital (LTACH) found that patients who required prolonged mechanical ventilation had significantly shorter median weaning times when weaned by unassisted breathing trials using a tracheostomy collar compared to using a pressure support wean (15 days vs. 19 days). However, they found that the two groups had no differences in 6-month mortality (56% vs. 51%) or 12-month mortality (66% vs. 60%).

Levine S, Nguyen T, Taylor N, et al: Rapid disuse of diaphragm fibers in mechanically ventilated humans. N Engl J Med 358:1327-1335, 2008.

Diaphragmatic biopsies from patients who met "brain-death" criteria and who underwent mechanical ventilation for 18 to 69 hours demonstrated greater muscle fiber atrophy compared with biopsies from subjects requiring mechanical ventilation for 2 to 3 hours during routine surgery.

Penuelas O, Frutos-Vivar F, Fernandez C, et al: Characteristics and outcomes of ventilated patients according to time to liberation from mechanical ventilation. Am J Respir Crit Care Med 184:430-437, 2011.

This multicenter international trial prospectively evaluated variables from patients in a weaning classification system that grouped patients by interval of time required to wean from mechanical ventilation; 55% of patients were classified as simple weaning, indicating they were able to be extubated on the same day that weaning was begun, and 6% required longer than 7 days to wean (prolonged weaning group).

See KC, Phua J, Mukhopadhyay A: Monitoring of extubated patients: are routine arterial blood gas measurements useful and how long should patients be monitored in the intensive care unit? Anaesth Intensive Care 38(1):96-101, 2010.

This observational study found that routine arterial blood gases drawn at 1 and 3 hours post-extubation did not improve detection of patients who needed restitution of respiratory support over the usual practice of clinical monitoring.

Stroetz RW, Hubmayr RD: Tidal volume maintenance during weaning with pressure support. Am J Respir Crit Care Med 152:1034-1040, 1995.

The study found that clinicians could not accurately predict who was ready for weaning based on clinical impressions alone, thus documenting the need for objective measurements.

Teixeira C, da Silva NB, Savi A, et al: Central venous saturation is a predictor of reintubation in difficult-to-wean patients. Crit Care Med 38(2):491-496, 2010.

This study of 73 patients in three mixed medical-surgical intensive care units showed that a drop in central venous saturation of >4.5% at 30 minute of breathing on a T-piece compared to baseline was an early and reliable variable that predicted reintubation with a sensitivity of 88% and specificity of 95%. Authors suggest that it be included in weaning protocols for difficult-to-wean patients.

Thille AW, Harrois A, Schortgen F, et al: Outcomes of extubation failure in medical intensive care unit patients. Crit Care Med 39:2612-2618, 2011.

This single center study describes a ventilator liberation failure rate of 15% after planned extubations. Patients who failed extubation did not have a greater severity of illness or longer time on the ventilator at the time of extubation, but they tended to be older and more likely to have chronic cardiac or pulmonary disease.

Tobin MJ: Extubation and the myth of "minimal ventilator settings." Am J Respir Crit Care Med 185:349-350, 2012.

This editorial by an international expert on weaning and mechanical ventilation emphasized that unloading effects on work of breathing by even low levels of pressure support or PEEP may be clinically important and the need for individualization of weaning processes and caution when extubating patients after breathing trials on low pressure support or PEEP or both.

Treger R, Pirouz S, Kamangar N, et al: Agreement between central venous and arterial blood gas measurements in the intensive care unit. Clin J Am Soc Nephrol 5(3):390-394, 2010.

This study found good correlation between central venous and arterial blood gas results in 40 patients who were admitted to a medical intensive care unit and supports use of the central venous blood gas measurement in most cases since the differences in pH, $PaCO_2$, and bicarbonate ion were not clinically significant.

CHAPTER 5

Sedation and Analgesia during Mechanical Ventilation

William D. Schweickert

Critically ill patients in intensive care units (ICUs) commonly experience pain, anxiety, agitation, and delirium as a by-product of their illness or supportive care or both. Patients undergoing mechanical ventilation are particularly at risk with common stressors including pain from intubation, procedures, and sacral pressure; anxiety about their surroundings and the inability to vocalize; and agitation from sleep deprivation, bed rest, and restraint created by tubes and devices. Nonpharmacologic therapies such as comfortable positioning in bed and verbal reassurance are reasonable initial considerations. However, the need for analgesic and sedative drugs to promote tolerance to the ICU environment is typically the rule in virtually all ICUs.

Analgesic and sedation needs vary widely in mechanically ventilated patients. Pain thresholds, anxiety levels, and noxious exposures are highly variable among patients. Furthermore, drugs administered to ICU patients frequently exhibit a wide range of pharmacokinetics and pharmacodynamics because of renal and hepatic dysfunction, drug interactions, low protein states, and shock (Chapter 17). As a result, analgesic and sedative drugs cannot be administered with a "one size fits all" approach. Instead, they should be titrated to discernible and reproducible clinical end points. Drugs used in this context are extremely potent, so clinicians must have heightened awareness of the potential for enduring effects and are encouraged to employ strategies that maximize symptom control while minimizing risk.

Data from both observational and randomized controlled trials demonstrate that sedation strategies can significantly impact both short- and long-term patient outcomes. When executed poorly, patients may suffer from extended delirium, excessive neurologic diagnostic testing, hemodynamic instability, prolongation of assisted ventilation, complications associated with immobility (e.g., joint contractures, sacral ulcers), and higher risk for psychiatric illnesses like posttraumatic stress disorder. In contrast, protocols with standardized symptom assessments that guide drug titration (for example, see Figure 37-E4) have yielded more patient days spent awake, shortened duration of mechanical ventilation, and reduced ICU and hospital lengths of stay. Additionally, selected studies of sedation (and exercise) protocols have improved physical and cognitive recovery, psychological well-being, and potentially survival.

This chapter emphasizes a systematic and protocol-based approach to sedation and analgesia during mechanical ventilation. The advantages of this approach over traditional care include (1) mechanically ventilated patients are more engaged and (2) symptom assessment is more feasible. Recognition of pain, anxiety, and delirium as independent contributors to patient distress enables a focused management strategy targeting these symptoms individually with appropriate medication.

Distress and Agitation

Distress is common during respiratory failure and may be generated by pain, dyspnea, anxiety, and delirium. Most mechanically ventilated patients experience some degree of *pain* even in

Additional online-only material indicated by icon.

the absence of surgical incisions or trauma (e.g., throat pain or discomfort from endotracheal intubation). Accordingly, clinicians must direct their initial attention toward analgesia when encountering nondescript patient distress. Untreated pain may cause many adverse effects including increased endogenous catecholamine release, myocardial ischemia, hypercoagulability, sleep deprivation, anxiety, and delirium. Treating this pain has been shown to ameliorate some of these effects.

Anxiety during mechanical ventilation stems from feelings of helplessness, the inability to predict upcoming events, and fear of death. These features may catapult preexisting anxiety and depression into a debilitating secondary disorder. Furthermore, anxiety and pain are inextricably linked: anxiety reduces the pain threshold and pain control may reduce anxiety.

Attention to *dyspnea* as an isolated cause for distress has intensified. Presentations span subjective complaints, elevated work of breathing, and severe ventilator asynchrony. These latter findings are particularly common in nontraditional ventilation strategies (low tidal volumes, permissive hypercapnia, and high-frequency oscillatory ventilation), which may contradict the body's usual response to stress. Modulating inspiratory flow rates to match neural demand, augmenting respiratory rates, or changing the mode of ventilation, such as from assist-control to pressure support, may relieve dyspnea in some instances (see Chapters 2, 3, and 47). Additionally, patients may express prominent dyspnea during weaning from prolonged mechanical ventilation (Chapter 25). Unfortunately, this may be unavoidable in patients with respiratory muscle weakness and advanced lung injury. Drug administration to facilitate tolerance is common in all of these scenarios.

Delirium is defined as an acute, reversible disturbance of consciousness and cognitive function that fluctuates in severity (Chapter 37). Its characteristics include defective perception, reduced short-term memory, confusion, disorientation, and, on occasion, hallucinations. Delirium is more recognizable when manifest as agitation; drug treatment to date has focused on managing the agitated state and avoiding self-harm. Hallmarks of agitation are repetitive, nonproductive movements. It is the most obvious, and dangerous, manifestation of distress. Akin to untreated pain, agitation can exert substantial oxygen consumption, risk myocardial ischemia and tachyarrhythmias, and result in patient self-injury via removal of life-sustaining devices.

Assessment of the Patient with Distress or Agitation

Assessing for distress and agitation should be a routine component of the bedside evaluation of patients. Semiquantitative scales, such as a visual analog pain scale (Figure 5.1), a behavioral pain scale (Table 5.1), and depth of sedation and severity of agitation (Table 5.2), should be used to facilitate communication among all ICU clinicians and to document the patient's status on the ICU flow sheet. The implementation of a regular and systematic assessment of distress with a consistent scale has been proven to minimize the amount of sedation necessary and speeds the recovery of the patient from a sedated state.

In general, evaluation should begin with observation of the patient's spontaneous interaction with the environment, including wakefulness, physical activity, and work of breathing coupled with ventilator synchrony. Intermittent mild agitation and breath stacking does not necessarily require pharmacologic suppression and can be a healthy response to avoid the dangers of strict

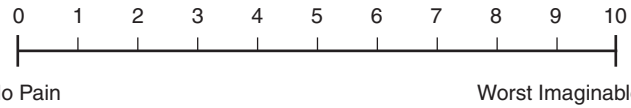


Figure 5.1 Typical visual analog pain scale (VAPS) in which patients are asked to indicate by voice or by pointing to where their pain is located on the scale. A score of 3 is usually acceptable in ICU patients.

TABLE 5.1 ■ **Behavioral Pain Scale for Assessing Pain in Noncommunicative, Mechanically Ventilated Adults**

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limb movements	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

Adapted from Payen JF, Bru O, Bosson JL, et al: Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 29(12):2258-2263, 2001.

TABLE 5.2 ■ **The Richmond Agitation and Sedation Scale: The RASS***

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
–1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
–2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
–3	Moderate sedation	Any movement (but no eye contact) to voice
–4	Deep sedation	No response to voice, but any movement to physical stimulation
–5	Unarousable	No response to voice or physical stimulation

Procedure to use the RASS in ICU patients:

1. Observe patient. Is patient alert and calm (score 0)?
   Does patient have behavior that is consistent with restlessness or agitation (score +1 to +4 using the criteria listed above under "Description")?
2. If patient is not alert, in a loud speaking voice state patient's name and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker.
   Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score –1).
   Patient has eye opening and eye contact, but this is not sustained for more than 10 seconds (score –2).
   Patient has any movement in response to voice, excluding eye contact (score –3).
3. If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response to shaking shoulder.
   Patient has any movement to physical stimulation (score –4).
   Patient has no response to voice or physical stimulation (score –5).

**Modified from Sessler CN, Gosnell M, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care patients. Am J Respir Crit Care Med 166:1338-1344, 2002; and Ely EW, Truman B, Shintani A, et al: Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA 289:2983-2991, 2003.*

bed rest and diaphragm passivity. Furthermore, nurses and physical therapists can harness this energy into exercise and mobilization. In contrast, severe agitation—which can be precipitous and unexpected—threatens placement of vascular catheters and access tubes. It can severely compromise respiratory and cardiovascular life support, increasing oxygen demand and generating carbon dioxide and lactic acid. Immediate assessment and intervention are necessary.

If, on examination, patients are not immediately awake, the clinician should attempt to engage them by voice alone. Should a response occur, one should briefly reassure patients of their location and inability to talk. Thereafter, one can ask the patients to follow a series of simple commands, such as opening their eyes and protruding their tongue. Facial gestures are optimal as advanced ICU-acquired weakness usually spares the facial neuromuscular axis (Chapter 48).

Further questioning should focus efforts on determining pain and other causes for distress. Use direct questions that intubated patients can answer "yes" or "no"; lip reading can be difficult and risks frustration for both the distressed patient and the clinician. Inconsistent responses and attention should prompt reassessment for delirium. If a patient is experiencing pain, anxiety, or dyspnea, the severity of distress should be evaluated on a scale of 0 to 10—for example, using a visual analog pain scale (see Figure 5.1). Quantitation of distress determines the urgency of treatment and guides drug dosing. These self-reports of pain are more reliable than the use of behavioral scales necessitated by the noncommunicative patient (Table 5.1). In contrast, vital signs are not reliable indicators for pain or control of distress, but they can guide clinicians to assess or reassess.

Patients unable to engage to voice have been coined "comatose" in the sedation literature. This delineation highlights the exceedingly deep level of sedation, usually necessary only in refractory cases of hypoxia, ventilatory failure, or in association with neuromuscular blockade. This depth of sedation prevents delirium assessment and purposefully has some negative connotation to promote reassessment of sedation down-titration. To gauge the depth of coma, a noxious physical stimulus can be applied briefly to elicit a physical reaction.

General Treatment Guidelines

At the outset of each day, the patient's nurse, physician, and (ideally) ICU pharmacist should agree on a desired goal of sedation depth and pain control for the day. A reliable standardized approach to describe depth of sedation is to use the Richmond Agitation and Sedation Score (RASS) shown in Table 5.2. In the earliest days of a patient's respiratory failure, this goal may be a moderate sedation depth—for example, a nonsustained eye opening to voice (e.g., RASS −2 to −3)—to facilitate ventilator synchrony and keep extra oxygen consumption to a minimum. As the patient recovers, a goal for an awake patient (e.g., RASS −1 to +1) is the standard. The ICU team should outline the agents for both persistent, moderate distress/agitation and optimal drug(s) for immediate rescue.

The choice of initial agent and the use of additional agents depend on the etiology of distress, the patient's clinical history including preexisting pain, psychiatric illness, and substance abuse. One recommended practice is to use an *opioid* to treat all endotracheally intubated patients receiving mechanical ventilation who are exhibiting mild to moderate levels of agitation or who communicate that they are having pain, anxiety, or dyspnea. The rationale for this practice is based on the inherent discomfort of the artificial airway coupled with the opioid's effectiveness at quelling air hunger.

In general, in patients *previously unexposed* to opioids, one can begin with low-dose, intermittent fentanyl, for example, 50 μg intravenous (IV) bolus, or another opioid of preference (Table 5.3). Frequent boluses should prompt consideration for initiating an infusion. One should titrate the dose to effect by giving additional bolus doses followed by increases in the maintenance infusion rate. As the infusion dose escalates, consider adding a sedative like propofol—ideally generating synergistic effects and less toxicity from each individual agent (Table 5.4).

For patients with moderate to severe distress, an individualized approach must be used based on the cause of the distress or agitation and the clinical urgency of the situation. If a quick, directed

TABLE 5.3 ■ **Intravenous (IV) Opioids Commonly Used during Mechanical Ventilation**

Drug	Initial IV Bolus Dose	Time to Onset	Metabolism	Comments
Fentanyl	50 μg–100 μg	< 1 min	CYP3A4 for first pass metabolism and active metabolites then cleared by kidney	Most common drug utilized for pain and agitation; accumulation occurs with prolonged infusions, particularly with renal dysfunction
Morphine	2–10 mg	5–10 min	Glucuronidation for first pass metabolism and active metabolites cleared by kidney	Histamine release risks more hypotension, urticaria, pruritus, flushing, and bronchospasm
Hydromorphone 0.7-4 mg		5–10 min	Glucuronidation for first pass metabolism, inactive metabolites	Consider for patients with refractory pain syndromes (high potency) and those with impaired renal function
Remifentanil 0.01-0.25 mcg/kg/min*		1–3 min	Nonspecific tissue esterases metabolize drug; no end-organ function required	Rapid elimination risks pain with drug discontinuation; reports of hyperalgesia; given as a continuous infusion—not a bolus

*= 0.6-15 mcg/kg/h given as a continuous infusion (no bolus).

examination does not reveal a correctable cause for agitation, such as an obstructed endotracheal tube or pneumothorax, empirical treatment with a high-dose opioid, propofol, benzodiazepine, or neuroleptic (Table 5.4) is indicated.

In general, there is no absolute upper limit to the dose of sedating drugs for mechanically ventilated patients. Indeed, uncommonly large doses (10 to 20 times usual) are sometimes needed to control agitation in this setting, particularly for patients who have acquired a tolerance to sedating drugs or have chronically used alcohol. The risk of adverse effects, however, increases with higher doses.

Formal protocols to guide drug administration, termed either "goal-directed" or "patient-targeted" sedation strategies, implement three main features: (1) applying a structured tool for the assessment of patient pain and distress (see Figure 5.1 and Tables 5.1 and 5.2), (2) setting a daily goal for depth of sedation and analgesia agreed upon by the nurse and physician, and (3) employing an algorithm that directs drug administration for both escalation and de-escalation based on the assessments that can be independently executed by the nurse. These protocols have yielded more success than specific analgesic and sedative selections. Proven benefits from clinical trials include shorter duration of mechanical ventilation, less dependence on tracheostomy, and reduced ICU and hospital lengths of stay. The primary mechanism of this finding is the (more) rapid return to an awakened state. Other factors may also be at play, including avoidance of protracted immobility, ileus, delirium, and self-injurious agitation.

Pharmacologic Treatment

Sedating drugs are psychoactive medications that exert a calming effect on thought or behavior. Medications commonly used for this purpose include benzodiazepines, opioids, neuroleptic agents, and IV anesthetics such as propofol. Opioids, given IV, are the mainstay for dyspnea and pain management. The optimal drug regimen for agitation and distress during mechanical ventilation in the ICU has not been determined. In theory, the ideal agent would provide adequate sedation and

TABLE 5.4 ■ **Intravenous Sedatives and Antipsychotics Commonly Used during Mechanical Ventilation**

Class of Drug	Drug	Initial Dose	Time to Onset	Metabolism	Comments
Benzodiazepine	Lorazepam	2–4 mg	5–20 min	Glucuronidation to inactive metabolites	Commonly associated with ICU delirium; when necessary, considered least toxic benzodiazepine for cirrhosis, as glucuronidation is preserved; propylene glycol toxicity possible with high-dose, continuous infusions
Benzodiazepine	Midazolam	2 –4 mg	2–5 min	CYP450 metabolism, active metabolites requiring renal clearance	Commonly employed for procedural sedation; can accumulate with infusions in advanced liver and renal disease
General anesthetic	Propofol	10–30 μg/kg/min infusion (no bolus)	1–2 min	CYP450 and glucuronidation to inactive metabolites; pharmacokinetics not significantly influenced by end organ dysfunction	Adjust feeds to account for lipid infusion, monitor triglycerides every 72 hours, consider surveillance for PRIS with CK, lactate, pH intermittent screening with prolonged infusions
α2 Adrenoceptor agonist	Dexmedetomidine	0.8 μg/kg/hour infusion (use of 1 μg/kg bolus is controversial)	5–10 min	Glucuronidation and CYP2A6 to inactive metabolites	FDA approval is for short-term infusion use (< 24 hours); recent trials have demonstrated safety and efficacy for longer infusion, particularly for patients requiring light sedation; bolus loading doses have been associated with substantial hypotension and many protocols elect against this use
Neuroleptic	Haloperidol	2–5 mg	5–15 min	CYP450 and glucuronidation to inactive metabolites	There is no FDA approval for intravenous use (IM, PO only); yet this is a long-standing practice in critical care; monitor QT_c interval with increasing doses; hold if QT_c interval > 500 msec

PRIS, propofol infusion syndrome; CK, creatinine kinase; FDA, Food and Drug Administration; QT_c, QT interval corrected for heart rate.

pain control with a rapid onset of action, rapid recovery after discontinuation, minimal systemic accumulation, and minimal adverse effects—without increasing *overall* health care costs.

Currently, reliance on short-acting agents (propofol) and intermediate and long-acting agents (benzodiazepines and opioids) is common practice, driven predominantly by familiarity and cost. Newer candidate drugs include ultra-short-acting drugs, such as remifentanil, or another class of agents, such as the α-2 adrenoreceptor agonist dexmedetomidine. Further studies of these drugs on outcomes such as duration of mechanical ventilation, length of ICU stay, mortality, and risk of delirium will help to establish their role in routine practice.

OPIOIDS TO TREAT DYSPNEA OR PAIN

Opioids are the preferred systemic agents to relieve pain. Additionally, limited published experience in other settings suggests that opioids may be the best agents for relieving dyspnea during mechanical ventilation. Opioids elicit their action through stimulation of the μ-, κ-, and δ-opioid receptors that are widely distributed within the central nervous system (CNS) and throughout the peripheral tissues. Stimulation of the μ1 sub-receptor inhibits the central nervous pain response. Interactions at other receptors contribute to adverse effects, including intestinal hypomotility, CNS depression, and hypotension (particularly in patients with high sympathetic tone). Respiratory system depression caused by opioids results from a breathing pattern with a reduction in respiratory rate and preservation of tidal volume ("slow and deep"). For the mechanically ventilated patient with ventilator asynchrony, an opioid is generally the preferred drug.

Opioids are divided into three primary classes based on chemical structure: (1) morphinan derivatives (morphine, hydromorphone); (2) phenylpiperidine agents (meperidine, fentanyl, remifentanil); and (3) diphenylheptanes (methadone) (see Table 5.3). Low cost and familiarity have made fentanyl, morphine, and hydromorphone the most commonly utilized opioids in the ICU. Individual selection from these three is generally guided by the desired onset of action, potency, and renal function. The high lipophilic nature of fentanyl provides it with a faster onset of activity via the IV route (which is almost immediate) than either morphine or hydromorphone (5 to 10 minutes for both). However, its high lipophilicity can lead to a prolonged duration of effect after repeated dosing or continuous IV infusion.

The IV route of administration for opioids is preferred in the critically ill as it provides a faster onset of activity, provides a high bioavailability, and affords better dose titratability. The oral, transdermal and intramuscular routes are not recommended in hemodynamically unstable patients given erratic drug absorption during low perfusion states and fever. All opioids have the potential to induce tolerance over time, resulting in the need for escalating doses to achieve the same analgesic effect. Patients may also show pseudotolerance—that is, escalating doses of opioid are needed to control a patient's pain because of an increase in extent or nature of the pain and not because of tolerance to the drug.

Ultra-short-acting opioids, such as remifentanil, are promising drugs with the potential to avoid prolonged effects and potentially reduce the amount of sedative required when compared with fentanyl and morphine. However, experiences of hyperalgesia—a paradoxical increased sensitivity to pain—can occur. Additionally, the rapid elimination risks either withdrawal or no analgesia rapidly after discontinuing the infusion. These characteristics make it an optimal drug for the operating theater, but they mandate more investigation for patients with enduring symptoms.

SEDATION FOR ANXIETY AND AGITATION

Benzodiazepines

Benzodiazepines act through the γ-aminobutyric acid (GABA) receptor, a neuroinhibitory receptor that causes neurons to be less excitable. These drugs have anxiolytic, sedative, amnestic, and

hypnotic effects at increasing doses. Traditionally, patients with anxiety that does not respond to nonpharmacologic measures have been treated with a benzodiazepine. However, some caution has been generated by observational data linking more prolonged exposures with higher rates of delirium. Benzodiazepines remain the preferred treatment for alcohol or sedative withdrawal and serve as an excellent rescue drug for severe agitation.

Because the anxiolytic efficacy and adverse effects of the commonly used IV benzodiazepines are similar, selection should be based primarily on pharmacokinetic considerations. Midazolam is often prescribed for procedural sedation because of its rapid onset and short half-life when used for such indications. In contrast, lorazepam is often the benzodiazepine of choice (should one be needed) in advanced liver disease, as glucuronidation remains preserved even in advanced cirrhosis. Intermittent IV dosing is generally always preferred, as continuous infusions have been associated with prolonged, excessive sedation and extended duration of mechanical ventilation.

The minimal duration of continuous IV treatment associated with the development of benzodiazepine dependence in critically ill patients is unknown because drug withdrawal symptoms are particularly difficult to distinguish from other causes of irritability, anxiety, and restlessness. Under these circumstances in patients recovering from a critical illness who have received a benzodiazepine continuously for longer than 1 to 2 weeks, one should taper the dose of benzodiazepine rather than withdraw it abruptly.

Propofol

Propofol, an IV anesthetic agent, is commonly used for patients requiring continuous sedative infusions during mechanical ventilation (Table 5.4). It exhibits sedative and hypnotic properties even at low doses and exhibits amnestic properties similar to benzodiazepines. Although its mechanism of action is not fully understood, propofol modulates neurotransmitter release, including GABA, with direct effects on the brain. This lipophilic drug quickly crosses the blood-brain barrier with an onset of action on the order of seconds to minutes. There is a rapid redistribution of propofol to the peripheral tissues, resulting in early recovery of consciousness after discontinuation of continuous infusions, even when administered for prolonged periods. Its rapid onset and offset of action provides a sedative option that is far more titratable than benzodiazepines and is considered the preferred sedative for patients in whom rapid awakening is important. High cost initially limited use of propofol for prolonged respiratory failure. Multiple studies comparing propofol with benzodiazepines consistently support the preferential use of propofol for shorter time to mental status recovery, shorter duration of mechanical ventilation, and cost effectiveness. Controversy remains as to whether propofol acts as an effective anticonvulsant, but it does reduce intracranial pressure after traumatic brain injury more effectively than opioids and decreases cerebral blood flow and metabolism.

Hypotension is common with propofol infusion as a result of decreases in venous and arterial tone and decreased cardiac output. The mandatory formulation of propofol in a lipid emulsion prompts two concerns. Triglycerides should be monitored every 3 to 7 days; the drug should be titrated down or stopped if the triglyceride level is > 500 mg/dL (> 5.65 mmol/L). Secondarily, because the lipid-rich emulsion supports bacterial growth, strict aseptic handling of the solution is critical. Finally, the *propofol infusion syndrome* (PRIS) is an uncommon adverse reaction characterized by metabolic acidosis, shock, rhabdomyolysis, and hyperkalemia. Originally described in children, evidence implicates a link between high doses administered for prolonged infusions. Although not proven to detect PRIS early, some clinicians check blood intermittently for creatinine kinase, pH, and lactate. To curb its likelihood, most centers prohibit propofol boluses during prolonged infusions and keep the infusion dose below 80 μg/kg/min. Fortunately, the occurrence of PRIS is rare in adults.

Central α Agonists

Drugs that stimulate α-2 adrenoceptors decrease noradrenaline release from both central and peripheral sympathetic nerve terminals. These effects, at both spinal and supraspinal sites, provide a combination of sedative and analgesic effect without the respiratory depressant effects of other sedatives or opioid drugs. Patients remain sedated when undisturbed but arouse readily with gentle stimulation. It produces an anxiolytic effect similar to benzodiazepines.

Dexmedetomidine is a highly selective α-2 agonist that the U.S. Food and Drug Administration (FDA) has approved for use only in short-term sedation (< 24 hours), such as in perioperative settings. Randomized controlled trials of longer-term infusions in ventilated patients have shown that it can provide light to moderate sedation but with mixed results when compared to other sedating agents. For example, in 2012 Jakob et al reported that dexmedetomidine, compared with midazolam, resulted in similar rates of neurocognitive events, including delirium, and fewer days of mechanical ventilation whereas, when compared to propofol, it had less risk of delirium and no difference in duration of mechanical ventilation. These trials also demonstrated a need for concomitant opioid administration for pain control. The drug's characteristic of sedation without respiratory depression makes it appealing to promote tolerance during noninvasive ventilation and to diminish anxiety during weaning from mechanical ventilation. Figure 87.2 in Chapter 87 illustrates one protocol for its usage in ICU patients.

The primary significant side effects of dexmedetomidine infusion are bradycardia and hypotension, which may be mitigated by avoiding a loading dose and initiating a slow infusion rate. In addition, a withdrawal syndrome characterized by agitation, tachycardia, and hypotension can result on discontinuation of a long-term infusion.

Drug De-escalation and Patient Mobilization

If the primary goal is to achieve the earliest awakening possible, an alternative rescue strategy is to use spontaneous awakening trials (SATs) ("daily interruption of sedation"). In this activity, unless contraindicated, any ongoing sedative or analgesic IV drug infusion is interrupted once daily to minimize the risk of excessive drug administration and accumulation. Patients are then assessed for the ability to tolerate complete drug discontinuation or transition to intermittent IV sedative dosing. Should the patient exhibit distress, clinicians administer IV bolus drug dosing to treat the symptoms, restart infusions as needed at half of the previous infusion dose(s), and titrate the drug to the desired depth of sedation. *Both* sedatives and analgesics should be interrupted once daily unless there is evidence for ongoing patient distress, reasonable certainty for ongoing pain, or utilization of neuromuscular blockade. Other contraindications include uncontrolled seizures, alcohol or benzodiazepine withdrawal, elevated intracranial pressure, and active myocardial ischemia.

Two randomized controlled trials have demonstrated that this strategy, particularly when awakening is paired with spontaneous breathing trials (SBTs) (Chapter 4), results in shorter duration of mechanical ventilation and ICU and hospital lengths of stay than traditional care. Concerns about the psychological and circulatory effects of the sudden interruption of sedation and analgesia have persisted, yet limited evidence has established no clear relationship to posttraumatic stress disorder or precipitating myocardial ischemia (although associated with a spike in catecholamine levels). However, the largest spontaneous awakening clinical trial did have a significantly higher rate of unplanned, self-extubation.

Once awakening is achieved, the opportunity to physically engage the patient becomes more possible. Several single-center trials have demonstrated that mechanically ventilated patients can safely undergo exercise and mobilization via physical therapy (Chapter 21). Standard protocols have patients progress through active range-of-motion exercises in bed, sitting at the edge of the

Clonidine, a less selective α agonist, has been used to augment the effects of general anesthetics and narcotics and to treat drug withdrawal syndromes in the ICU. Administered only orally or transdermally coupled with substantial hypotension and bradycardia, its applicability during mechanical ventilation is limited.

NEUROLEPTIC DRUGS

Neuroleptic or antipsychotic drugs are employed for symptoms of agitation, usually in the context of delirium. Typical antipsychotics, like haloperidol (see Table 5.4), block dopamine receptors in the brain and lead to tranquility. They reduce initiative and interest in the environment as well as manifestations of emotion. Patients are typically drowsy and slow to respond to external stimuli. In contrast to other sedatives, the absence of hemodynamic derangement or respiratory suppression can make the drug particularly appealing in certain circumstances. However, the antidopaminergic actions can also result in extrapyramidal side effects such as dystonia, akathisia, and pseudoparkinsonism. These conditions can usually be reversed with diphenhydramine or benztropine.

Atypical antipsychotics, such as quetiapine, risperidone, olanzapine, and ziprasidone, block both dopamine and serotonin receptors, with a higher ratio of serotonin than dopamine blockade. They may be as effective as haloperidol with less risk of extrapyramidal symptoms (particularly in drugs with high serotonin-to-dopamine blocking ratios) but further comparative studies are needed to clarify how best to use such agents.

Another dose-dependent toxicity of neuroleptics includes prolongation of the QTc interval with potential for inducing *torsades de pointes* and cardiac arrest (Chapter 34). Accordingly, some providers limit total (IV) dosing to less than 40 mg per day and monitor the QTc interval regularly. Doses should be held until the QTc interval is less than 500 msec. The *neuroleptic malignant syndrome*, characterized by fever, muscle rigidity, and autonomic dysfunction, is a rare, idiosyncratic complication of any neuroleptic agent that must be recognized early to prevent death. Bromocriptine, dantrolene, and benzodiazepines can be used for treatment.

OTHER AGENTS

Ketamine, a nonbarbiturate phencyclidine derivative, binds with *N*-methyl-D-aspartate (NMDA) and sigma opioid receptors to produce intense analgesia and a state termed *dissociative anesthesia*—patients become unresponsive to nociceptive (painful) stimuli but may keep their eyes open and maintain their reflexes. Blood pressure, laryngeal reflexes, and drive to breathe are maintained. Popularity is limited by its undesirable side effect of hallucinations, emergence delirium, and unpleasant recall, increased oral secretions, lacrimation, tachycardia, and the potential for exacerbating myocardial ischemia. Some studies have used it in conjunction with opioids to diminish the latter's side effects, especially gut hypomotility.

Inhaled volatile anesthetics, such as isoflurane and sevoflurane, have been used in the operating theater for many years but not in the ICU because of the inability to conserve the volatile gases. New devices, designed to recycle the anesthetic drug, make these drugs more feasible for ICU use. These anesthetics have a better pharmacokinetic profile than many IV sedatives and have demonstrated quicker, more reliable time to awakening, extubation, and ICU discharge in the postoperative setting.

bed with legs dangling, active transfers, and, finally, ambulating. These activities have been shown to be feasible and safe with an endotracheal tube (as opposed to tracheotomy), even in the earliest days of mechanical ventilation.

Published trials of early mobilization in the patient with respiratory failure have shown shorter times to getting patients out of bed, ambulating, and leaving the hospital with an improved functional status compared to usual care. A randomized controlled trial pairing sedative interruption with early physical and occupational therapy additionally demonstrated significant reductions in the duration of mechanical ventilation and delirium. How these short-term functional gains translate into longer-term outcomes remains to be measured. Finally, emphasis on devices to facilitate patient exercise and muscle stimulation has grown exponentially. Bedside cycle ergometers, transcutaneous electrical stimulation, and walking platforms are all currently under investigation.

An annotated bibliography can be found at www.expertconsult.com.

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This two-center, randomized controlled trial demonstrated that early exercise and mobilization conducted during a protocol of sedative minimization resulted in improved patient physical functional performance at hospital discharge, shorter duration of mechanical ventilation, and reduced delirium duration when compared to usual care.

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Strom T, Martinussen T, Toft P: A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet 375:475-480, 2010.

This single center, randomized trial of patients undergoing mechanical ventilation for more than 24 hours demonstrated that patients managed with bolus opioid administration alone—in contrast with opioid bolus with tailored sedation—had shorter duration of mechanical ventilation and ICU and hospital lengths of stay.

CHAPTER 6

Use of Neuromuscular Blocking Agents

Meghan B. Lane-Fall ■ Benjamin A. Kohl ■ C. William Hanson III

Neuromuscular blocking drugs (NMBDs) have been used in clinical practice since 1935 when d-tubocurarine was first isolated. NMBDs are most commonly employed in the operating theater to immobilize patients and enhance surgical exposure. Pharmacologic paralysis is now considered an important adjunct to the management of the critically ill patient in a variety of disease states in the intensive care unit (ICU). The intensivist who uses NMBDs should understand the indications and contraindications for their use, the pharmacodynamics and pharmacokinetics of the available agents, their possible interactions with other drugs, and complications associated with their use in the ICU.

It is imperative for ICU care providers to remember that NMBDs have *no* intrinsic sedating or analgesic activity and that paralyzed patients must always be given sedatives such as opioids or benzodiazepines prior to the initiation of neuromuscular blockade. Similarly, in patients who are receiving continuous pharmacologic paralysis, there should be frequent assessment and acknowledgment by all care providers regarding the adequacy of underlying sedation. How this is measured in the paralyzed patient is controversial (adjusted dose, frequent cessation of neuromuscular blockade, cerebral monitors, etc.). Some have advocated for continuous bispectral index monitoring despite the lack of studies in the ICU that have shown superiority of this method over any other. Finally, although pharmacologic paralysis is rarely desired, its use is sometimes necessary. When prolonged paralysis is warranted, the minimum total dose (dose administered × length of time) should be the goal. Many intensive care units that use therapeutic paralysis monitor the depth of neuromuscular inhibition with a peripheral nerve stimulator. When used, the dose of muscle relaxant should be titrated to maintain one to two twitches out of a "train-of-four."

Physiology of Neuromuscular Excitation

Neural excitation commences within the nerve body. The neural impulse is then propagated along the axon of a motor neuron, as a result of ion-regulated membrane voltage differentials. As the signal reaches the nerve terminal, it is converted and transmitted by means of a chemical messenger across a synapse to a motor unit. The neuromuscular synapse consists of the nerve terminal, the synaptic cleft (20 to 50 μm wide), and the motor end plate on the muscle. The neural signal stimulates the release of chemical messengers that then cross the synapse and bind to receptors on the motor unit. Upon binding to its postsynaptic receptor, ion flux is stimulated, a membrane voltage differential ensues, and electrical transmission resumes in the motor unit.

Acetylcholine (ACh) is the primary chemical messenger responsible for mediating neuromuscular transmission. ACh serves as the messenger not only for neural communication at the neuromuscular junction but also for many central nervous system pathways, autonomic ganglia, and postganglionic parasympathetic nerve endings. When a nerve impulse arrives at the nerve

terminal of the neuromuscular junction, intracytoplasmic vesicles containing ACh fuse with the nerve cell membrane, and the contents are released into the synapse. The ACh binds to the nicotinic ACh receptor (AChR) on the muscle cell, causing a conformational change and increasing the cellular permeability to sodium. When a sufficient number of sodium channels open, the transmembrane potential exceeds –50 mV and, as a result, the membrane depolarizes, creating an action potential that propagates to the entire motor unit and results in muscular contraction. The process of contraction requires calcium and is inhibited by magnesium.

The termination of physiologic depolarization follows diffusion of free ACh from the synaptic cleft, unbinding of ACh from the postganglionic receptor, and degradation of the ACh molecule by the membrane-bound enzyme acetylcholinesterase. Acetylcholine is hydrolyzed to acetate and choline, which are reabsorbed into the nerve terminal, reconstituted to ACh by the enzyme choline acyltransferase, and repackaged into intracytoplasmic vesicles.

Mechanism of Neuromuscular Blocking Drugs

There are two general categories of NMBDs with effects at the neuromuscular junction: depolarizing and nondepolarizing neuromuscular blocking agents.

DEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS (D-NMBDs)

Depolarizing neuromuscular blocking agents (of which succinylcholine is the sole agent currently available for clinical use) act as ACh receptor agonists. The initial effect of D-NMBD binding is depolarization followed by muscle contraction. The blockade that follows contraction is caused by the relatively slow hydrolysis of the drug relative to that of ACh. Persistence of the D-NMBD at the receptor site renders adjacent sodium channels inactive. Repolarization is therefore delayed, and successive nerve impulses find the muscle refractory to depolarization.

Succinylcholine is used to achieve rapid (<60 seconds) paralysis and is frequently used for patients who are at risk for regurgitation of gastric contents during emergent intubation. Recovery from the paralytic effects of succinylcholine is also rapid because of rapid degradation of the drug by butyrylcholinesterase. This "rapid on, rapid off" effect is particularly beneficial for spontaneously breathing patients in whom positive pressure ventilation might be detrimental or in cases where securing the airway via endotracheal intubation may be difficult and rapid resumption of spontaneous ventilation is desired. Succinylcholine in rare instances can be delivered by a continuous infusion but is usually not used for prolonged paralysis in critically ill patients.

Of note, succinylcholine has potentially dangerous cardiac side effects that may preclude its use in some critically ill patients. Arrhythmias caused by autonomic stimulation (via nicotinic receptors on both sympathetic and parasympathetic ganglia) include sinus tachycardia, sinus bradycardia, junctional rhythms, and sinus arrest. Marked hyperkalemia following succinylcholine administration can lead to ventricular fibrillation or asystole. In most individuals, an increase in serum potassium level of 0.5 mEq/L is expected. This rise in serum potassium results from the depolarization of ACh receptors (primarily extrajunctional) and subsequent potassium release from muscle cells. Patients who have sustained denervation injuries or disorders (e.g., spinal cord transection, amyotrophic lateral sclerosis [ALS]) may have a much larger increase in serum potassium concentration, to the point of hyperkalemic cardiac arrest, if given succinylcholine. Patients with recent burns and muscular dystrophies are also at risk of life-threatening hyperkalemia after succinylcholine. Although renal failure per se is not a contraindication to succinylcholine use, its use is contraindicated in patients with hyperkalemia resulting from renal failure or other etiologies (e.g., digoxin toxicity [see Chapters 39 and 81]). Labeling by the Food and Drug Administration (FDA) also indicates cautious use in patients with renal failure because of prolongation of the blockade.

NONDEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS

Nondepolarizing neuromuscular blocking drugs (*ND-NMBDs*) do not depolarize the motor end plate but act as competitive inhibitors of ACh at the postsynaptic nicotinic receptor. ND-NMBDs work by binding the ACh receptor (thus blocking ACh) without inducing the conformational change that normally permits passage of sodium ions. ND-NMBDs in clinical use include pancuronium, vecuronium, rocuronium, and cisatracurium. These drugs have different side effects (e.g., pancuronium can cause tachycardia as a result of its vagolytic effects), metabolism, and duration of action (Table 6.1). Differences in the duration of action relate to mechanisms of drug clearance, which is particularly important in critically ill patients with multiple organ dysfunctions. ND-NMBDs may be used if prolonged paralysis in the ICU is warranted, although tachyphylaxis has been reported with prolonged exposure. More recently, rocuronium (an ND-NMBD) has emerged as an alternative to succinylcholine when rapid paralysis (60 to 90 seconds) is required and succinylcholine is contraindicated.

Drug and Electrolyte Interactions

Neuromuscular transmission is affected by myriad factors including other drugs (e.g., aminoglycosides, corticosteroids, and calcium channel blockers all augment the neuromuscular blocking effects), acid-base balance (acidemia augments neuromuscular blockade and alkalemia tends to attenuate it), and electrolyte imbalances (e.g., hypocalcemia, hypokalemia, and hypermagnesemia prolong blockade). Of note, patients who are maintained on or who have recently been given antiepileptic drugs (e.g., phenytoin, carbamazepine) demonstrate accelerated recovery from blockade and frequently require higher and more frequent doses to maintain neuromuscular blockade.

TABLE 6.1 ■ **Nondepolarizing Neuromuscular Blocking Drugs Used in the ICU**

Name of Drug	Clearance Mechanism	Intermittent Dosage	Infusion Dosage	Comments
Pancuronium	Renal excretion > hepatic metabolism	Initial: 0.05–0.1 mg/kg Subsequent: 0.01–0.1 mg/kg	Initial: 0.1 mg/kg/h Range: 0.06–0.4 mg/kg/h	Rapid onset; long-acting; boluses are likely to cause tachycardia (which may be severe) Active metabolite accumulates in renal failure
Vecuronium	Hepatic metabolism > renal excretion	Initial: 0.08–0.1 mg/kg Subsequent: 0.05–0.1 mg/kg	Initial: 1 μg/kg/min Range: 0.8–1.2 μg/kg/min	Rapid onset; short-to-intermediate duration of action; negligible hemodynamic effects Active 3-desacetyl metabolite accumulates in renal failure and can cause prolonged paralysis
Cisatracurium	Plasma cholinesterase; nonenzymatic degradation	Initial: 0.15–0.2 mg/kg Subsequent: 0.03 mg/kg	Initial: 3 μg/kg/min Range: 0.5–10 μg/kg/min	Intermediate onset; short duration of action; no effects on nicotinic, autonomic receptors, or muscarinic cardiac receptors; may cause histamine release when given rapidly in high dosage

CLINICAL INDICATIONS FOR PHARMACOLOGIC PARALYSIS IN THE ICU

The use of lung protective ventilation in the acute respiratory distress syndrome (ARDS) is the only proven intervention that has been shown to significantly decrease mortality of this disorder in a large, randomized, multicenter clinical trial compared to traditional high tidal volume ventilation. The ability to keep plateau pressures at or below 30 cm H_2O in a lung that is progressively noncompliant can be challenging. Decreasing the tidal volume delivered by the ventilator to patients with ARDS will decrease the end-inspiratory pressure (i.e., the plateau pressure). When this is not successful, changing the mode of ventilation to one that is pressure-controlled may suffice (see Chapters 73 and 74). However, despite different ventilator settings and heavy sedation, one may be unable to provide adequate oxygenation or ventilation or both to a patient with severe ARDS while maintaining plateau pressure ≤30 cm H_2O (or the plateau pressure measurement is inaccurate because of the patient's continued inspiratory efforts at a rapid respiratory rate. In such cases, a trial of pharmacologic paralysis is warranted.

Moderate hypothermia has now become standard of care for patients who show a return of spontaneous circulation (ROSC) within 60 minutes of cardiac arrest but who remain unconscious (see Chapter 49). Shivering is common, particularly during the induction of hypothermia, and, if left untreated, significantly increases both metabolic rate and oxygen demand. Such an increase in metabolic activity amplifies the risk for adverse myocardial events. Neuromuscular blockers are indicated during the hypothermic phase if shivering cannot be controlled by other pharmacologic means. If a neuromuscular blockade is used, continuous electroencephalography (EEG) should be considered as hypothermia decreases seizure threshold and clinical diagnosis becomes difficult.

Traumatic brain injury (TBI) represents another scenario in the ICU where neuromuscular blockade may be indicated. Although routine paralysis is not a first-line strategy to reduce elevated intracranial pressure (ICP), its use should be considered in cases of refractory intracranial hypertension unresponsive to conventional therapy. In situations where coughing, straining, or dyssynchrony are contributing to impaired intracranial venous drainage or raised arterial pressure, immediate neuromuscular blockade must be considered to enhance cerebral perfusion.

Finally, myriad scenarios arise in both surgical and medical ICUs where chemical paralysis is warranted to ensure the safety of a patient. Situations where such a strategy might be useful include patients with an open chest or abdomen or unstable fractures where small movements may worsen the initial injury. Additionally, there are situations where protection of a patient's airway may be extremely tenuous and slight movements risk dislodging the artificial airway. All of these scenarios are best managed first with a structured sedation regimen; however, pharmacologic paralysis may become necessary and should be readily available if conventional measures fail.

COMPLICATIONS OF NEUROMUSCULAR BLOCKING DRUGS

Several studies have shown that infusions of NMBDs for more than 24 hours have deleterious effects not seen when used for shorter periods of time. For example, NMBDs that were developed to be short acting have been shown to have active metabolites that accumulate and may prolong the duration of action (see Table 6.1). Conversely, patients may acquire tolerance or resistance to NMBDs when treated for extended periods, requiring higher than usual doses (tachyphylaxis).

Syndromes of prolonged weakness can follow administration of NMBDs to critically ill patients. This can be due to the accumulation of active metabolites, a progressive neuropathy of critical illness, changes in the function or anatomy of the neuromuscular junction, or development of a critical illness neuropathy or myopathy or both (see Chapter 48). NMBDs should be administered only when they are clearly necessary and with particular caution if the patient is also receiving high-dose corticosteroids (e.g., in the treatment of status asthmaticus or a chronic obstructive pulmonary disease [COPD)] flare) (see Chapters 75 and 76). Increasing sedation or

changing sedatives (e.g., using propofol) may be an acceptable alternative to the use of paralysis in the ICU in some patients (see Chapter 5).

No method of administration or use of a particular NMBD can entirely prevent development of the syndrome of prolonged weakness or the development of a critical illness–associated myopathy. Acquired weakness in the ICU is often multifactorial and although administration of neuromuscular blocking agents, both alone and in combination with corticosteroids, have been shown to be associated with acquired ICU weakness, much remains unknown. There is general consensus, however, that prolonged muscle disuse contributes to further atrophy and is associated with adverse long-term outcomes. As a result, intermittent dosing of NMBDs has become a much more common practice than continuous infusion because it allows for intermittent partial recovery of muscle function.

Frequent reassessments of the need for neuromuscular blockade and a multidisciplinary approach to optimizing sedation are necessary in the critically ill patient requiring paralysis. Daily "holidays" from the NMBD should be considered in a manner similar to the practice of holding sedatives during the morning to assess their continued need (Chapter 5). Termination of NMBD should occur once it is safe for the patient to be maintained on a sedation regimen alone.

An annotated bibliography can be found at www.expertconsult.com.

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Chamorro C, Borrallo JM, Romera MA, et al: Anesthesia and analgesia protocol during therapeutic hypothermia after cardiac arrest: a systematic review. Anesth and Analg 110(5):1328-1335, 2010.

This review article compared approaches to sedation, analgesia, and paralysis in the setting of therapeutic hypothermia after cardiac arrest. Sixty-eight ICUs were represented in the studies evaluated, and the authors found significant variability in the sedative, analgesic, and paralytic regimens. The authors called for efforts to reach consensus about how to address sedation in this population.

Forel JM, Roch A, Papazian L: Paralytics in critical care: not always the bad guy. Curr Opin Crit Care 15(1):59-66, 2009.

This review article predates the randomized controlled trial of cisatracurium in early ARDS but was written by two of the same authors. In this paper, the authors discussed how neuromuscular blockers affect pulmonary mechanics and oxygen exchange. The prevalence of NMB use in ARDS management was mentioned, as was the putative role of NMB in causing or exacerbating myopathy associated with critical illness.

Hunter JM: New neuromuscular blocking drugs. N Engl J Med 332(25):1691-1699, 1995.

This is a review article describing basics of neuromuscular transmission, depolarizing versus nondepolarizing neuromuscular blockers, and anticholinesterase reversal agents. Chemical structures, pharmacokinetics, and pharmacodynamics of neuromuscular blockers are also presented.

Kim MH, Hwang JW, Jeon YT, et al: Effects of valproic acid and magnesium sulphate on rocuronium requirement in patients undergoing craniotomy for cerebrovascular surgery. Br J Anaesth 109(3):407-412, 2012.

Patients undergoing cerebrovascular surgeries were randomized to valproic acid, valproic acid plus magnesium, or control. The amount of neuromuscular blocker required to maintain adequate intraoperative paralysis was highest in the group allocated to receive valproic acid. Bolus followed by infusion of magnesium attenuated the neuromuscular resistance seen with valproic acid alone.

Latronico N, Bolton CF: Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. Lancet Neurol 10(10):931-941, 2011.

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Marsch SC, Steiner L, Bucher E, et al: Succinylcholine versus rocuronium for rapid sequence intubation in intensive care: a prospective, randomized controlled trial. Crit Care 15(4), 2011.

This is a single-center randomized trial of succinylcholine versus rocuronium for intubation in critically ill patients. Despite using a lower than usual dose of rocuronium for rapid sequence intubation (0.6 mg/kg used instead of 1.2 mg/kg), there was no difference in rates of hypoxemia or failed first intubation attempts. Intubating conditions were achieved in 81 seconds with succinylcholine versus 95 seconds with rocuronium.

Papazian L, Forel JM, Gacouin A, et al: Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 363(12):1107-1116, 2010.

This was a multicenter, randomized, double-blind, placebo-controlled trial comparing neuromuscular blocker (cisatracurium) versus placebo in the management of patients with ARDS. Patients were included if they had ARDS for fewer than 48 hours and received either cisatracurium or placebo for 48 hours. Survival and ventilator-free days improved in the cisatracurium group, and there was no difference in myopathy between the groups.

Patel SB, Kress JP: Sedation and analgesia in the mechanically ventilated patient. Am J Respir Crit Care Med 185(5):486-497, 2012.

This is a review article discussing recent advances in ICU sedation and analgesia. Objective assessments of pain, sedation, and agitation were presented that enable titration of sedating medications to meaningful end points. The article also explained context-sensitive half-time, the concept that the half-life of infused drugs depends on the duration of the infusion, and the pharmacokinetic properties of the drug.

Warr J, Thiboutot Z, Rose L, et al: Current therapeutic uses, pharmacology, and clinical considerations of neuromuscular blocking agents for critically ill adults. Ann Pharmacother 45(9):1116-1126, 2011.

This is a review article that presents indications for use of neuromuscular blockers in critical care. Discussed applications of NMB include: "immobilizing patients for procedural interventions, decreasing oxygen consumption, facilitating mechanical ventilation, reducing intracranial pressure, preventing shivering, and management of tetanus." The article also compared the dosing and pharmacokinetic properties of commonly used neuromuscular blockers.

CHAPTER 7

Assessment and Monitoring of Hemodynamic Function

Amy J. Reed ■ C. William Hanson III

The goal of monitoring hemodynamic parameters in critically ill patients is to allow for the rapid diagnosis of tissue malperfusion and help guide therapy. This assessment can be difficult to quantify, as hemodynamic variables considered normal in most individuals may in fact be suboptimal for the critically ill patient. Therefore, hemodynamic assessment must take into account the pathophysiology particular to each patient as well as incorporate inferences of tissue perfusion from physical exam and other objective data such as lactate, SvO_2, or urine output. Newer monitoring modalities to ascertain tissue perfusion are being developed, but their clinical applicability in the intensive care unit (ICU) remains uncertain.

Mean arterial pressure (MAP; Box 7.1, Equation 1) is the most commonly used estimate of tissue perfusion pressure. However, this assumption is subject to several important limitations, measurement accuracy notwithstanding. First, the range of values considered adequate (i.e., MAP of 60 to 70 mm Hg) is based on normal physiologic conditions and may be inappropriate in patients who have a need for higher (i.e., baseline hypertension, concern for spinal cord ischemia) or lower (i.e., leaking aortic aneurysm) pressures. Second, MAP is a measurement taken at the arterial level (radial, brachial, femoral) that may or may not adequately represent the resistance at the tissue microvascular level. Overreliance on this value may result in impaired tissue perfusion despite mean arterial pressures that are seemingly "normal." Third, the capability for critically ill patients to autoregulate and maintain tissue perfusion within a limited MAP range is often attenuated with severe illness.

Basic Physiologic Components

PRESSURES, VOLUMES, COMPLIANCE, AND RESISTANCE

Hemodynamic variables are either directly measured or calculated. Volume can be estimated through sonographic modalities (e.g., inferior venal caval diameter, left atrial diameter), but it is usually inferred from other indices. Intravascular pressure and volume are related by compliance (Box 7.1, Equation 2). The compliance of any system is directly related to its intrinsic distensibility. Vessels or chambers that are highly distensible, such as the systemic venous bed, can accommodate large changes in volume with small changes in pressure. In contrast, the systemic arterial circuit is much less distensible (stiffer) and thus far less compliant than the systemic venous circuit. Specifically, systemic veins are approximately 25 times more compliant than systemic arteries. The systemic venous circuit of a typical adult contains about 2500 mL at an average central venous pressure of about 10 mm Hg, whereas the systemic arterial circuit contains only about 750 mL at a mean arterial pressure of about 100 mm Hg. Although compliance can be measured using imaging techniques, this is rarely done in the ICU setting. However, variations in compliance can have important implications for recruitable reserve volume.

Resistance, on the other hand, is a frequently discussed hemodynamic parameter in critically ill patients. Resistance reflects the propensity of vessels to resist blood flow, relating pressure to flow. It is calculated from pressures measured within the system in addition to flow through the system (cardiac output) (Box 7.1, Equations 3 and 4). Acute changes in vascular resistance are frequently multifactorial and can have profound effects on arterial blood pressure. Although capacitance and resistance are conceptually independent, and indeed the main resistance vessels (arterioles) are distinct from the capacitance vessels (venous plexus), in reality, the mechanisms that increase vascular resistance also usually decrease capacitance.

MEASUREMENTS WITHIN THE CIRCUIT

The circulatory system can be divided into a pulmonary (right) and systemic (left) system comprising three elements arranged in series: a reservoir, pump, and resistor. For the right-sided circulation, the reservoir consists primarily of the veins (systemic veins, venules, and venous sinuses). The pump is the

BOX 7.1 ■ Hemodynamic Equations

Equation 1: MAP ≈ 1/3 (SBP – DBP) + DBP

MAP = mean arterial blood pressure
SBP = systolic blood pressure
DBP = diastolic blood pressure

Equation 2: Compliance = change in volume/change in pressure ($\Delta V/\Delta P$)

Equation 3: PVR = {(mean PAP – PAWP)/CO} × 80

where PVR = pulmonary vascular resistance expressed in traditional units (dyne•sec cm^{-5})
mean PAP = mean pulmonary artery pressure (mm Hg)
PAWP = pulmonary artery wedge pressure (mm Hg)
CO = cardiac output (L/min)

Equation 4: SVR = {(mean AP – CVP)/CO} × 80

where SVR = systemic vascular resistance expressed in traditional units (dyne•sec cm^{-5})
mean AP = mean systemic arterial pressure (mm Hg)
CVP = mean central venous pressure (mm Hg)
CO = cardiac output (L/min)

Equation 5: CI = CO/BSA

where CI = cardiac index (L/min•m^2)
CO = cardiac output (L/min)
BSA = body surface area (m^2)*

Equation 6: Pressure (mm Hg) = pressure (cm H_2O) × 1.36

Equation 7: The Fick equation: CO = $\dot{V}o_2/(Cao_2 - C\bar{v}o_2)$

where CO = cardiac output (L/min)
Vo_2 = oxygen consumption per minute (mL/min)
Cao_2 = oxygen content of arterial blood (mL/L)†
$C\bar{v}o_2$ = oxygen content of mixed venous blood (mL/L)†

Equation 8: Cardiac output = amount of indicator injected/area under curve

** See Mattar JA: A simple calculation to estimate body surface area in adults and its correlation with the Du Bois formula. Crit Care Med 17:846-847, 1989, for estimating BSA from height and weight and online calculators of BSA.*

† One must convert from traditional units of oxygen content (mL/dL) to mL/L.

right ventricle, and the resistor is the pulmonary arterial system (predominantly pulmonary arterioles). Similarly, for the left-sided circulation, the reservoir consists of the pulmonary veins and left atrium, the pump is the left ventricle, and the resistor is the systemic arterial circulation (predominantly arterioles).

These variables can be measured or calculated through a variety of approaches. Using a pulmonary artery catheter and systemic arterial blood pressure monitor, one can measure pressures in both circuits as well as flow through the entire circulation. Cardiac output and other hemodynamic variables are commonly corrected for variations in body size by indexing the values to the body surface area (BSA) (Box 7.1, Equation 5). The pressure in the systemic venous reservoir is reflected by the central venous pressure (CVP) and right atrial pressure (RAP). The latter is the proximate source of right ventricular filling during diastole and, when measured at the appropriate time in the cardiac cycle, can estimate the right ventricular end-diastolic pressure (RVEDP)—that is, the right ventricular preload. The tip of the pulmonary artery catheter measures the pressure in the pulmonary artery or one of its branches. The resistance in the pulmonary arterial circuit can be calculated if the cardiac output, mean pulmonary arterial pressure, and left atrial pressure (estimated as the pulmonary artery occlusion or wedge pressure, PAOP or PAWP) are known (Box 7.1, Equation 3). This equation represents the general hydraulic relationship in which resistance to fluid flow through a system equals the pressure drop across the system divided by the mean flow.

The PAWP normally reflects the pressure in the pulmonary venous reservoir, which is the source of left ventricular filling during diastole—that is, left ventricular preload. Systemic arterial blood pressure, cardiac output, and CVP can similarly be used to calculate systemic vascular resistance (Box 7.1, Equation 4). The range of normal pressures is shown in Table 7.1, and the range of normal flows and resistances are given in Table 7.2.

TABLE 7.1 ■ **Normal Values of Hemodynamic Pressures (Under Unstressed Conditions)**

Location	Mean (mm Hg)	Range (mm Hg)
Right Atrium		
Mean	3	1–5
Right Ventricle		
Peak systolic	25	17–32
End diastolic	4	1–7
Pulmonary Artery		
Mean	15	9–19
Peak systolic	25	17–32
End diastolic	10	4–13
Occlusion pressure	7	2–12
Left atrium	7	2–12
Left Ventricle		
Peak systolic	125	100–140
End diastolic	9	5–12
Aorta		
Mean	100	70–105
Peak systolic	125	100–140
End diastolic	84	60–90

From Pepine CJ, Hill JA, Lambert CR (eds): Diagnostic and Therapeutic Cardiac Catheterization. Baltimore: Williams & Wilkins, 1998.

TABLE 7.2 ■ **Normal Values for Selected Cardiovascular Parameters**

Parameters (Units)	Abbreviation	Mean	Range
Cardiac output (L/min)	CO	6	5.2–7.4
Cardiac index (L/min•m^2)	CI	3.2	2.6–4.2
Left ventricular stroke volume (mL)	LVSV	82	70–94
Left ventricular stroke volume index (mL/m^2)	LVSVI	49	30–65
Systemic vascular resistance (dyne•sec cm^{-5})	SVR	1130	900–1460
Pulmonary vascular resistance (dyne•sec cm^{-5})	PVR	205	100–300
Oxygen consumption index (mL/min•m^2)	$\dot{V}O_2$	134	113–148

From Pepine CJ, Hill JA, Lambert CR (eds): Diagnostic and Therapeutic Cardiac Catheterization. Baltimore: Williams & Wilkins, 1998.

Hemodynamic Measurements

SYSTEMIC BLOOD PRESSURE

There are a myriad of devices, both invasive and non-invasive, available to calculate blood pressure. Non-invasive oscillometric devices have replaced auscultatory sphygmomanometers in most hospital settings. However, intermittent blood pressure measurement may be insufficient in certain critically ill patients. In such patients, intra-arterial catheters may be placed for continuous hemodynamic monitoring. Arterial catheterization may also be appropriate when frequent arterial blood samples are necessary (i.e., to monitor arterial oxygenation or acid-base status). As with any device, the risk-to-benefit ratio should be frequently reassessed.

Intravascular pressure devices measure pressure in reference to some arbitrary ("zero") point. This reference point, typically the level of the left atrium, is estimated as the midaxillary line in a supine patient. By establishing this point as "zero," the atmospheric pressure is ignored and any change in pressure reflects that of the vessel being monitored. Traditionally, blood pressure is reported in millimeters of mercury (mm Hg), whereas certain other pressures—for example intracranial pressures—are frequently given in centimeters of water (cm H_2O). (Equation 6 of Box 7.1 can be used to convert mm Hg to cm H_2O based on the specific gravity of mercury.)

Intra-arterial blood pressure monitoring provides not only an absolute blood pressure measurement, but also an arterial flow waveform that can be informative. The flow within the aorta is biphasic with a systolic and diastolic phase separated by an incisura. Blood flows forward during the systolic phase as a result of cardiac ejection. The incisura represents the slight retrograde flow of blood during aortic valve closure. The upstroke during diastole is due to elastic rebound of the arterial walls. The normal waveform changes as it travels distally because of multiple factors, including damping and increased impedance. One change is that the incisura evolves into the wider dicrotic notch. In general, as the arterial pressure is measured more peripherally, the systolic and pulse pressures increase (associated with a narrowing of the waveform). Importantly, though the systolic blood pressures in the periphery are higher than in central vessels, the *mean* arterial pressures measured peripherally are comparable to those measured centrally. The character of the arterial waveform is determined to a major extent by the stroke volume and the compliance of the arterial tree and to a lesser extent by the character of systolic ejection. A "spiky" waveform with a prominent dicrotic notch in the setting of low blood pressure suggests intravascular volume depletion. A sharp systolic upstroke with a prominent pulse pressure is characteristic of a noncompliant vascular circuit (i.e., atherosclerosis). These findings apply in both the pulmonary and systemic arterial circuits.

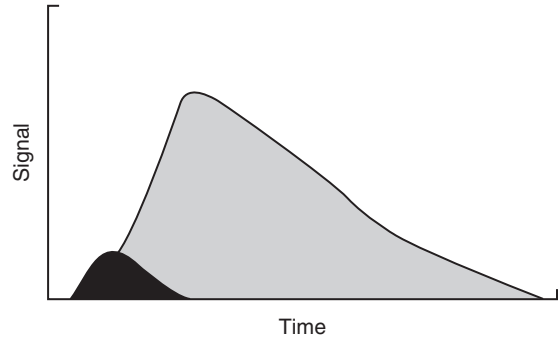


Figure 7.1 Cardiac output indicator (indocyanine green or thermal indicator signal) curves for low (gray) and high (black) cardiac output. The high cardiac output curve peaks sooner (because of a shorter transit time) and has less area under the curve because of more rapid transit of the indicator past the sensor.

CARDIAC OUTPUT

Various methods and devices, both invasive and non-invasive, are used to estimate cardiac output. The estimates of cardiac output and other parameters by non-invasive (or minimally invasive) devices are inaccurate in many pathophysiologic settings, and invasive methods remain the gold standard for rigorous hemodynamic monitoring. Perhaps no other hemodynamic measurement device has come under as much scrutiny as the pulmonary artery catheter (PAC). Heavily debated over utility versus risk, the PAC in repeated studies has failed to demonstrate a significant advantage to its use in terms of changing clinically important outcomes (e.g., mortality or ICU length of stay). Notwithstanding, the PAC is still routinely used in many critically ill patients and indeed is the gold standard against which newer cardiac output monitors are compared. The debate surrounding use of a PAC reinforces the concept that the risk-to-benefit ratio must be considered when using any invasive monitor in the ICU, including the pulmonary artery catheter. It also emphasizes the need for all invasive monitors to be used for specific indications and for finite times, with frequent reevaluation of their usefulness in each ICU patient.

Within the circulatory system, cardiac output dictates the adequacy of blood flow. The standard method used to quantify flow through the circulation relies on an indicator dilution (washout) technique. Although the indicator was originally a dye, a thermal signal (cold normal saline) is generally used in clinical practice. As used in a PAC, the indicator is introduced just proximal to the right atrium (in the superior or inferior vena cava) and sampled in the pulmonary artery near the distal tip of the PAC. By detecting blood temperature by means of a thermistor near the distal tip of the PAC in the pulmonary artery (after all the blood has mixed and equilibrated within the right ventricle), the device can estimate the flow. Rapid washout of the indicator occurs in high cardiac output states, whereas delayed washout indicates the reverse (Figure 7.1). The area under a "concentration versus time" curve is inversely proportional to the cardiac output (the descending limb of the washout curve is extrapolated electronically) (Box 7.1, Equation 8). Lithium can also be used as an indicator for estimating cardiac output, although this requires a specialized arterial blood pressure monitoring electrode to measure lithium levels.

In current practice, cardiac output is often measured continuously using a method of thermal dissolution. A thermal filament embedded within a pulmonary artery catheter generates pulses of heat every 30 to 60 seconds. Blood temperature downstream at the distal tip of the catheter is measured by a thermistor, and cardiac output is calculated as noted earlier and displayed as a time averaged value over a fixed number of minutes. Transpulmonary thermodilution is an alternative, somewhat less invasive, method of estimating cardiac output based on the dissolution of tracer from a central venous (as opposed to pulmonary artery) catheter to a central arterial (femoral, brachial, or axillary) catheter. The accuracy of these methods is highly dependent on specificity of measurement as well as physiology (Table 7.3). For example, if the injectate volume is half of what it should be,

TABLE 7.3 ■ **Errors in Performing Thermodilution Cardiac Outputs with Associated Effects on Estimates of Cardiac Output**

Error	Error in Estimation of Cardiac Output
Volume of injectate < "correct" volume	Overestimates
Injectate is cooler than reference probe	Overestimates
Injectate is warmer than reference probe	Underestimates
Indicator injected too slowly	Overestimates
Large volume of intravenous fluid being given simultaneously via a central venous catheter	May overestimate or underestimate
Slowing of heart rate due to cold injectate	Underestimates (by up to 10%)
Tricuspid regurgitation with exposure of indicator to greater volume of blood	Overestimates (faster washout)
Tricuspid regurgitation with slow release of tracer from right atrium	Underestimates (prolongs descending part of injectate curve)
Left-to-right intracardiac shunt	Early recirculation of cold blood/dye interferes with analysis of descending limb of injectate curve
Right-to-left intracardiac shunt	Overestimates (loss of indicator)
Low body (33–34°C) or high ambient temperature	Variable (increased signal:noise ratio)
Very low cardiac output	Variable (difficulty extrapolating descending limb of injectate curve)

the calculated cardiac output will be twice that of the correct value. Some physiologic perturbations can also result in error such as tricuspid regurgitation or septal defects. In patients with these conditions, the Fick equation (Box 7.1, Equation 7) should more accurately estimate cardiac output.

Like the thermodilution method, the Fick method requires the presence of a pulmonary artery catheter (to obtain the blood sample representing mixed venous blood from the pulmonary artery). The Fick method is less popular than the thermodilution method for routine use in the ICU for a number of reasons. The automated thermodilution method is easier to use for making repeated measurements, both in following patients over time and decreasing variability. Disadvantages of the Fick method are the cumbersome need for replicate measurements, obtaining blood samples, and the cost of measuring oxygen content. Furthermore, if oxygen consumption is substantially different from the assumed 200 to 250 mL/min or is not at a steady state (both of which can be common in critically ill patients), the absolute value of the calculated cardiac output by the Fick method will be inaccurate as an absolute value. Despite this drawback, it may still provide potentially useful data for trends and responses to interventions.

Less invasive methods of estimating cardiac output are becoming more prevalent. Several rely on proprietary analysis of the arterial waveform pulse contour as investigators have shown that stroke volume is proportional to arterial waveform pulsatility. Calibration for vascular compliance is accomplished using patient biometrics in concert with waveform analysis or against standard methods of CO measurement (i.e., transpulmonary thermodilution). Although promising, these technologies are heavily dependent on software systems that are still being developed and validated under varying clinical conditions. Furthermore, alterations in vascular tone, intravascular volume, arrhythmias, and ventilatory mechanics can all affect arterial pulse contour and thereby interfere with the accuracy of these measurements. This may limit the applicability of these approaches particularly in those critically ill patients in whom cardiac output monitoring is important in guiding therapy.

Several sonographically based volumetric methods are available to measure cardiac output. Transesophageal or transthoracic echocardiography permits direct visualization of cardiac chambers. By

measuring volumetric changes between systole and diastole, stroke volume and cardiac output can be estimated. Alternatively, Doppler ultrasonography, measuring blood flow velocity in the descending aorta, can be used to estimate cardiac output in conjunction with the cross-sectional area of the aorta. This technique is limited in its ability to act as a continuous monitor over a prolonged period of time and requires specialized equipment and experience that is not universally available. Electrical bioimpedance can also be utilized to non-invasively estimate cardiac output. This technology is based on the fact that liquid has a higher conductance than does tissue. As such, the impedance to a small voltage applied across the thorax should decrease in proportion to the stroke volume ejected into the aorta. Using an algorithm that takes into account several bio-indices (i.e., sex, age) as well as measured variables (i.e., hematocrit, electrolytes), one can estimate a cardiac output. However, there is currently no general consensus on the clinical applicability of this method when used in critically ill patients.

CENTRAL VENOUS PRESSURE (CVP)

Despite the enormous growth in technology and medical device innovation, the intravascular volume status of critically ill patients often remains uncertain. Physical exam is notoriously unreliable in this population, and non-invasive measures are often uninformative or misleading and, when relied on solely to guide treatment, can potentially be deleterious. Although direct ultrasonographic visualization (i.e., of cardiac filling) can sometimes provide useful information, it is often impractical and, if not used by properly trained individuals, can similarly be misleading. Cannulation of a central vein for measuring central venous pressure (CVP) is often utilized to help determine intravascular volume status.

Given the relatively compliant nature of the venous vascular system, the CVP is assumed to reflect the volume of blood in the systemic venous reservoir. A CVP approaching 0 mm Hg likely reflects hypovolemia, whereas a CVP of 25 mm Hg usually indicates the opposite. However, because of the number of factors in critically ill patients that increase either intrathoracic pressure (i.e., mechanical ventilation, pleural effusions, pulmonary dysfunction) or abdominal pressures (i.e., surgery, bowel edema, abdominal hypertension, obesity), the absolute value of the CVP must be considered in light of a patient's entire clinical picture. As is often the case with many physiologic variables, it is of greater significance to trend CVP than to act based on a solitary value, particularly when the CVP falls within an intermediate range (5 to 12 mm Hg).

The change in CVP in the setting of fluid challenge, as opposed to its use as a static variable, has been proposed as an indicator of volume status. If the CVP increases substantially in response to an adequate volume challenge (i.e., 5 to 10 mL/kg predicted body weight [PBW] of normal saline given over 30 minutes or autotransfusion from a passive leg raise test), this suggests that the systemic venous reservoir is relatively noncompliant and therefore replete. Conversely, when the CVP shows little or no response to such a volume load, intravascular volume depletion is more likely. The same inferences apply to the response of the PAWP by a volume challenge. Employing a goal-defined strategy for volume resuscitation is often useful. The goal can be either a physiologic end point (i.e., systemic blood pressure, cardiac index, mixed venous oxygen saturation) or a clinical end point (i.e., urine output) in combination with physical exam. It is important to remember, however, that because the venous system is designed for compensation in maintaining hemodynamic homeostasis (that is, it can "offload" the remaining circulatory system because of its high compliance), whereas central venous pressures may provide information at the ends of the spectrum, it is often indeterminate as a measure of euvolemia.

AN INTEGRATED APPROACH

Any given hemodynamic index in isolation is of limited utility. Addressing parameters that fall outside of a "normal" range without a comprehensive view of the patient's cardiovascular and

metabolic requirements can, at best, be temporizing and, at worst, harmful. Measurement of hemodynamic variables must be interpreted within the context of the clinical situation and goals of care. Understanding the interplay between the various components of the cardiovascular circuit and developing a systematic approach to addressing physiologic perturbations is critical to optimal therapeutic intervention.

When subjective or objective evidence of malperfusion as suggested by end-organ dysfunction exists, the relative insufficiency of the systemic arterial blood pressure must be considered. The therapeutic approach to hypotension can often be guided by clinical situation (i.e., ongoing bleeding) and may not warrant further investigation. However, when the reasons underlying hypotension are unclear, or if arterial blood pressure is unresponsive to initial therapy, more investigation and monitoring may be indicated to help determine the pathophysiology or guide resuscitation. As technology advances, so too does the ability to more precisely define physiologic processes. However, treatment directed at normalizing a number may not translate into improved outcomes, as "normal" is a relative and dynamic concept during critical illness.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 8

Cardiogenic Shock and Other Pump Failure States

Frank E. Silvestry

Although acute circulatory shock occurs as a consequence of a wide variety of conditions, all result in inadequate oxygen delivery to the organs, tissues, and cells, relative to the oxygen requirements of their metabolic activities. The final common pathway of all shock states is an imbalance between oxygen supply and demand. The effects of inadequate tissue perfusion are initially reversible, but prolonged end-organ hypoperfusion leads to cellular hypoxia and the derangement of critical biochemical processes, including (1) cell membrane ion pump dysfunction, (2) intracellular edema, (3) leakage of intracellular contents into the extracellular space, and (4) inadequate regulation of intracellular pH. These abnormalities rapidly become *irreversible* and result sequentially in cell death, end-organ damage (multiple organ system failure), and death. As a result, the prompt recognition of shock and initiation of therapy are imperative. Despite modern aggressive treatment in the intensive care unit (ICU) setting, the mortality rates from shock remain very high—for example, mortality rates of 50% to 80% are reported for patients with acute myocardial infarction and cardiogenic shock.

Cardiogenic shock occurs when impairment of cardiac pump function results in inadequate tissue perfusion. This chapter focuses on the pathophysiology, clinical diagnosis, and approach to the patient with cardiogenic shock; Chapter 9 discusses shock resulting from low preload, and Chapter 10 discusses shock resulting from the maldistribution of blood flow. Pericardial tamponade and major pulmonary embolus, the two primary causes of *obstructive shock,* are presented in Chapters 54 and 77, respectively. Chapter 52 addresses acute heart failure syndromes that overlap with cardiogenic shock with regard to specific etiologies.

Pathophysiology

DETERMINANTS OF TISSUE PERFUSION

The principal determinants of tissue perfusion are cardiac output and arterial blood pressure. Cardiac output is defined by the relationship in Equation 1 (Box 8.1). Factors that affect ventricular stroke volume include preload, intrinsic myocardial contractility, and afterload (Figures 8.1 to 8.4). Arterial blood pressure represents the driving force for tissue perfusion and can be defined by Equations 2 and 3 (see Box 8.1). Systemic vascular resistance is principally determined by the arterioles. Shock can be caused by a variety of pathophysiologic processes that alter any of these factors, thereby reducing oxygen delivery to the tissues, and these can be organized by hemodynamic alteration as shown in Table 8.1.

STAGES OF SHOCK

The shock syndrome is characterized by a series of physiologic stages beginning with an initial inciting event that causes acute circulatory compromise. Shock may subsequently progress through three stages, culminating in irreversible end-organ damage and death.

BOX 8.1 ■ Basic Hemodynamic Equations

Equation 1. CO = SV × HR

CO = cardiac output (L/min)
SV = ventricular stroke volume (L/beat)
HR = heart rate (beats per minute [bpm])

Equation 2. MAP = (CO × SVR) + CVP

MAP = mean arterial blood pressure (mm Hg)
CVP = central venous pressure (mm Hg)
CO = cardiac output (L/min)
SVR = systemic vascular resistance
where SVR (in units of mm Hg/L/min) × 80 = SVR (in units of dyne sec cm^{-5})

Equation 3. MAP = DBP + 1/3 (SBP – DBP)

DBP = diastolic blood pressure (mm Hg)
SBP = systolic blood pressure (mm Hg)

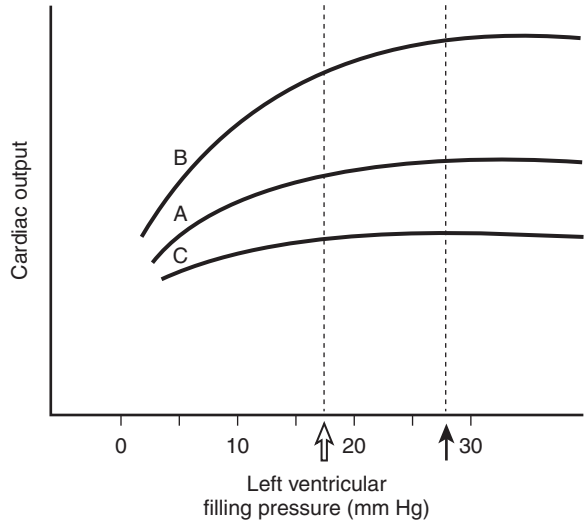


Figure 8.1 "Starling curves" of ventricular function representing the relationship between cardiac output (as the dependent variable) and left ventricular filling (end-diastolic) pressure (LVEDP) (as the independent variable) for myocardial states of normal *(A)*, enhanced *(B)*, and decreased *(C)* myocardial contractility. Other important independent variables that determine cardiac output, such as afterload (see Figure 8.3), are held constant. In the intensive care unit, LVEDP is normally approximated by pulmonary artery wedge pressure (PAWP). The dashed vertical line at ~18 mm Hg *(open arrow)* indicates the PAWP at which fluid begins to accumulate in the interstitial space of the lung. The dotted vertical line at ~28 mm Hg *(closed arrow)* indicates the PAWP at which acute alveolar edema develops. Note that all curves lack "descending limbs" at high filling pressures (i.e., decreasing cardiac outputs at high LVEDP). Descending limbs of Starling curves are considered to be experimental artifacts and may have been due to development of mitral regurgitation at high distending pressures. *(See Elzinga G: Starling's "Law of the heart": Rise and fall of the descending limb. News Physiol Sci 7:134-137, 1992, for more details about the descending limb.)*

Preshock

Preshock is also known as compensated shock. During this stage, the body's homeostatic mechanisms rapidly compensate for diminished perfusion. Reflex sympathetic activation leads to tachycardia and peripheral vasoconstriction, thereby temporarily maintaining blood pressure and cardiac output.

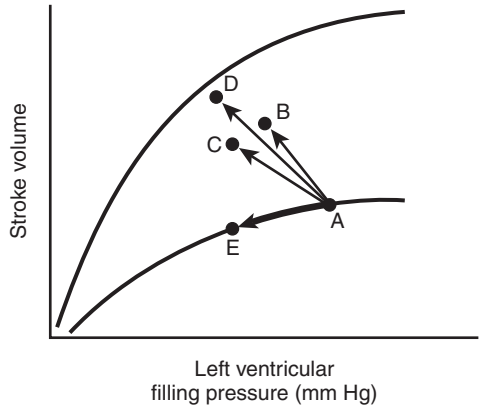


Figure 8.2 Curves relating stroke volume and left ventricular end-diastolic pressure (LVEDP) at states of normal and depressed contractility. At an elevated LVEDP on the lower curve *(point A)*, administration of an inotropic agent (e.g., dopamine) increases contractility *(point B)* and causes a modest decrease in preload (e.g., lower LVEDP). Likewise, administration of a vasodilator agent (which reduces both afterload and preload) results in improved stroke volume but with a greater decrease in LVEDP *(point C)*. Concomitant treatment with both agents produces an additional increase in stroke volume *(point D)*. In contrast, treatment with a diuretic alone decreases LVEDP with no increase in stroke volume *(point E)*. *(Modified from Cohn JN, Franciosa JA: Vasodilator therapy of cardiac failure. N Engl J Med 297:27-31, 1977.)*

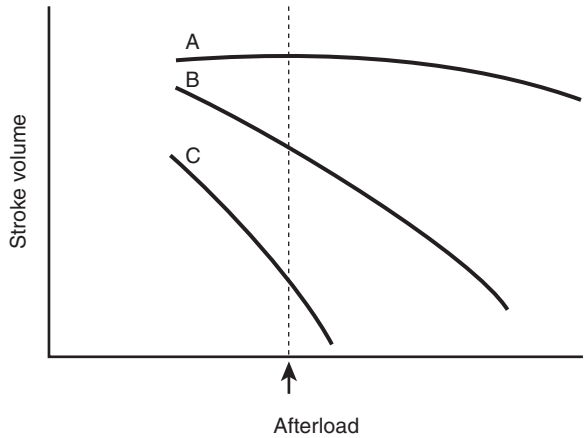


Figure 8.3 Curves representing the relationship between stroke volume (SV) (as the dependent variable) and left ventricular afterload (as the independent variable) for states of normal myocardial function *(A)*, and moderate *(B)* and severe *(C)* myocardial dysfunction. Other variables affecting stroke volume, such as preload, are constant. When myocardial function is normal, SV is relatively preserved (curve A) as afterload increases above normal *(dashed line, closed arrow)*, but SV decreases markedly (curves B and C) when myocardial dysfunction is present. *(Modified from Cohn JN, Franciosa JA: Vasodilator therapy of cardiac failure. N Engl J Med 297:27-31, 1977.)*

Frank Shock

During this stage, the regulatory mechanisms become overwhelmed, and signs and symptoms of organ dysfunction begin to appear, including tachycardia, tachypnea, metabolic acidosis, and oliguria. The emergence of these signs typically corresponds to one or more of the following: (1) a 25% reduction in effective blood volume in hypovolemic shock, (2) a decrease in the cardiac index to less than 2.5 L/min/M^2, or (3) activation of the many mediators of the sepsis syndrome (Chapter 10).

Irreversible Shock

During this stage, progressive end-organ dysfunction leads to irreversible organ damage and eventual death: (1) urine output may decline and renal failure may ensue; (2) mental status may become altered, with agitation, obtundation, and eventually coma; (3) respiratory muscle fatigue may be precipitated by decreased perfusion of the diaphragms, leading to hypercapnic respiratory failure; and (4) multiple organ system failure may ensue.

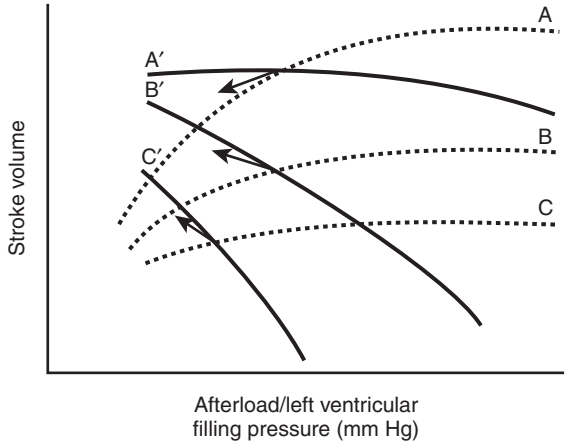


Figure 8.4 Three Starling curves *(dotted lines)* relating stroke volume and left ventricular filling pressure with normal *(A)*, moderately decreased *(B)*, and severely decreased *(C)* myocardial function (Figure 8.1) are superimposed on three curves *(solid lines)* relating stroke volume and afterload for the same three states of myocardial function (normal, *A′*; moderately decreased, *B′*; and severely decreased, *C′*) (Figure 8.3). Because most vasodilator agents (e.g., nitroprusside) reduce both preload and afterload, their effects on stroke volume depend on the state of myocardial function. For example, when myocardial function is normal, such a vasodilator lowers stroke volume because of the predominant effect caused by lowering preload (as shown by the arrow originating at the intersection of curves A and A′). In contrast, when myocardial function is depressed, such an agent results in improved stroke volume despite a decrease in preload (arrows from the intersections of curves B and B′ and curves C and C′) (similar to point C in Figure 8.2). *(Modified from Cohn JN, Franciosa JA: Vasodilator therapy of cardiac failure. N Engl J Med 297:27-31, 1977.)*

TABLE 8.1 ■ **Various Shock States and Typical Results of Pulmonary Artery Catheterization**

Cause of Shock	Cardiac Output	RA and RV Pressures	PAWP	SVR	Mixed Venous Saturation
Hypovolemic (low preload)	↓	↓	↓	↑	↓
Distributive (low afterload)	↑, WNL, ↓	WNL, ↓	WNL, ↓	↓↓	WNL, ↑
Obstructive (major PE)	↓	↑	WNL	↑	↓
Obstructive (tamponade)	↓	↑	↑	↑	↓
Cardiogenic (LV failure)	↓	↑	↑↑	↑	↓
Cardiogenic (acute MR)	↓	WNL, ↑	↑	↑	↓
Cardiogenic (RV infarction)	↓	↑	WNL	↑	↓
Cardiogenic (acute VSD)	WNL	↑	WNL, ↑	↑	↑

RA, right atrial; RV, right ventricular; PAWP, pulmonary artery wedge pressure; SVR, systemic vascular resistance; ↓, decreased; ↓↓, markedly decreased; ↑, increased; ↑↑, markedly increased; WNL, within normal limits; PE, pulmonary embolus; LV, left ventricular; MR, mitral regurgitation; VSD, ventricular septal defect.

Differential Diagnosis

To initiate appropriate therapy, cardiogenic shock must be differentiated from other categories of shock, such as hypovolemic shock, distributive (low afterload) shock, or obstructive shock. The clinical history, physical examination, and laboratory finding should provide important clues to the shock state's origin. The use of a balloon-tipped, flow-directed pulmonary artery (Swan-Ganz) catheter can facilitate the initial categorization of the shock state as well as help to identify the individual causes of cardiogenic shock (see Table 8.1 and Box 8.2). Echocardiography with Doppler can provide similar, although more limited assessment of these parameters as well.

Hypovolemia, occurring as a result of blood loss or volume depletion, results in inadequate ventricular preload with resultant decreased stroke volume and cardiac output. Typically, filling pressures (such as the central venous pressure [CVP] and pulmonary artery wedge pressure [PAWP]) are reduced, as is cardiac output. Similarly, impaired left ventricular filling from increased intrapericardial pressure resulting from cardiac tamponade or obstruction to right ventricular outflow secondary to acute massive pulmonary embolism results in reduced left ventricular preload, stroke volume, and cardiac output. Initial treatment is with volume infusion until more definitive therapy is initiated. In patients with left ventricular systolic dysfunction, diastolic dysfunction, or right ventricular dysfunction, "normal" filling pressures may not be adequate to maintain normal cardiac output. Thus, relative hypovolemia may be present despite a "normal" CVP or PAWP. The ideal filling pressures in patients with heart failure are those that allow maximal cardiac output without producing pulmonary edema. Often, patients with chronic heart failure require a PAWP of 16 to 20 mm Hg to maintain adequate cardiac output.

Shock caused by vasodilation or low afterload is termed *distributive shock* (e.g., shock caused by sepsis or anaphylaxis). Septic shock occurs as a result of endogenous and exogenous biologically

BOX 8.2 ■ Causes of Cardiogenic Shock

Myocardial Causes

- Left ventricular systolic dysfunction
  - —Acute myocardial infarction (see Chapter 50)
  - —Acute myocarditis
  - —Cardiomyopathy
  - —Myocardial contusion caused by trauma
  - —Sepsis with myocardial depression
- Left ventricular diastolic dysfunction
  - —Hypertrophic cardiomyopathy
  - —Ischemic left ventricle
- Right ventricular dysfunction
  - —Acute right ventricular infarction

Arrhythmias

- Bradyarrhythmia (complete heart block) (see Chapter 33)
- Tachyarrhythmia (ventricular tachycardia) (see Chapter 34)

Mechanical Problems

- Acute valvular disease
  - —Aortic dissection with aortic regurgitation (see Chapter 51)
  - —Endocarditis with acute mitral regurgitation or aortic regurgitation
  - —Papillary muscle dysfunction, infarct, ischemia, rupture with severe mitral regurgitation
- Left ventricular outflow obstruction
  - —Hypertrophic obstructive cardiomyopathy
- Acute ventricular septal defect postmyocardial infarct

active factors, which produce vasodilation and impair oxygen delivery to the tissues. Early septic shock may be associated with increased cardiac output secondary to decreased afterload and increased heart rate, but late septic shock may be associated with profound reduction in cardiac output from myocardial depression resulting from a number of factors. Late septic shock needs to be distinguished from primary cardiogenic shock because the therapy for these conditions differs significantly.

Clinical Pearls and Pitfalls

EARLY DIAGNOSIS

A high index of suspicion is required to appropriately diagnose cardiogenic shock in its early stage and rapidly initiate therapy. Although cardiogenic shock is readily diagnosed when frank hypotension develops, a compensatory elevation in systemic vascular resistance may serve to maintain arterial blood pressure despite a profound reduction in cardiac output and end-organ perfusion. Thus, "preshock" should be suspected when there is evidence of low cardiac output, despite normal or near-normal systemic arterial pressures. Increased heart rate, cool and clammy skin on the extremities with a reticulated (net-like) pattern (livedo reticularis) and slow capillary filling (> 2 sec) (measured at fingertips), a decrease in urine output, and altered mental status are important clues to a reduced cardiac output that may precede frank hypotensive shock. The initial evaluation of patients with suspected cardiogenic shock should include a rapid assessment of organ perfusion and volume status (Figure 8.5).

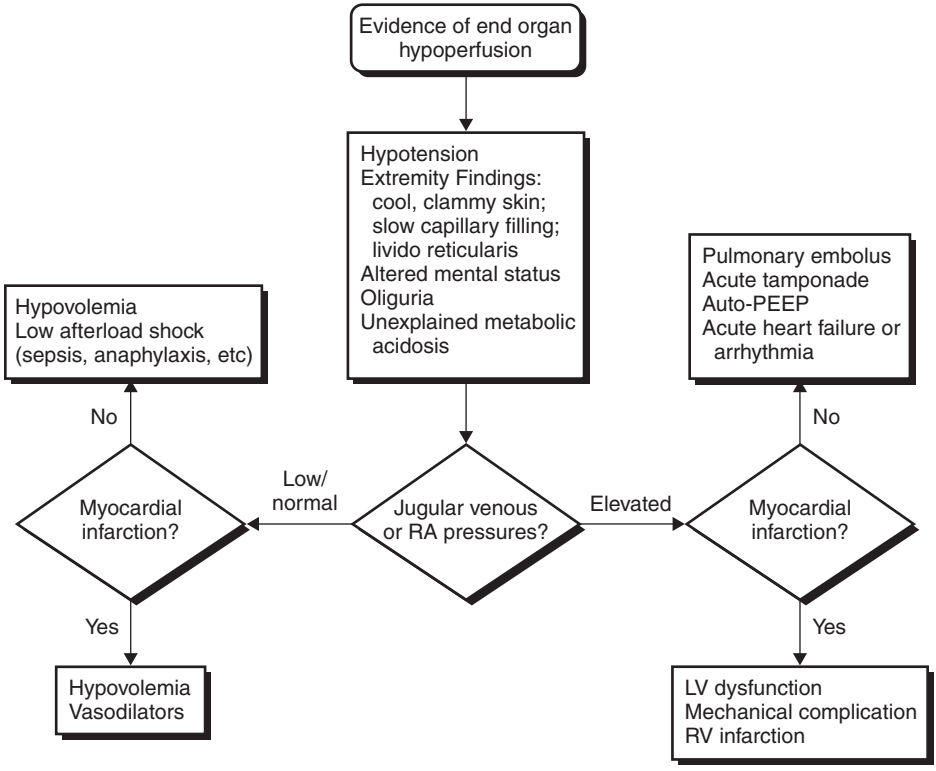


Figure 8.5 Algorithm for evaluation and management of patients with evidence of end-organ perfusion with circulatory shock. PEEP, positive end-expiratory pressure; RA, right atrial; LV, left ventricular; RV, right ventricular.

Pulse oximetry or arterial blood gas (ABG) analysis should be done to assess oxygenation as well as a chest radiograph to assess possible pulmonary congestion. An electrocardiogram (ECG) should be performed to look for evidence of myocardial infarction or cardiac ischemia or dysrhythmia.

An echocardiogram is extremely helpful in differentiating patients with cardiogenic shock caused by left ventricular dysfunction from those with right ventricular infarction, ventricular septal rupture, acute mitral regurgitation, and cardiac tamponade. Echocardiography can also identify patients with low preload or low afterload states, largely by the presence of a careful assessment of left and right ventricular chamber size and ejection fraction as well as estimating the degree of collapse of the inferior vena cava during the respiratory cycle. Flow-directed pulmonary artery catheterization can be used to differentiate cardiogenic shock from other categories (see Table 8.1). It can also guide volume therapy because many patients in shock require higher than normal filling pressures to maintain an adequate cardiac output.

Myocardial Infarction and Cardiogenic Shock

IMPAIRED LEFT VENTRICULAR FUNCTION

The primary pathophysiologic disturbance in cardiogenic shock is compromised cardiac function. Although a variety of cardiac processes can cause cardiogenic shock (see Box 8.2), it most often occurs as a consequence of acute myocardial infarction (MI) causing sudden severe left ventricular dysfunction. Cardiogenic shock commonly results when there is loss of a critical quantity (usually > 40%) of left ventricular myocardial mass. Postinfarction cardiogenic shock remains the leading cause of in-hospital mortality in patients with acute MI.

A large acute MI may lead to impaired pump function with a resultant decrease in stroke volume and arterial blood pressure. Abnormalities of diastolic function occur with acute ischemia and result in elevated intracardiac pressures, pulmonary congestion, reduced left ventricular filling, and further reductions in left ventricular preload and stroke volume. Ultimately, progressive hypotension potentiates ischemia and initiates a downward vicious spiral, resulting in irreversible hypotension and death (Figure 8.6).

Cardiogenic shock complicates 7% to 8% of all acute MIs and, as myocardial necrosis progresses, shock often develops after hospitalization. In 89% of patients in whom cardiogenic shock developed in the first Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO I) study (a trial of thrombolytic strategies in acute MI), shock developed *after* hospital admission. Risk factors for the development of cardiogenic shock with acute MI include advanced age, preexisting left ventricular ejection fraction < 35%, diabetes, and a history of a prior MI. Mechanical complications of acute MI, such as acute ventricular septal rupture and acute papillary muscle rupture with mitral regurgitation, typically occur 2 to 7 days after the initial event. Therefore, sudden hemodynamic deterioration several days after admission should prompt a rapid search for one of these mechanical complications.

The mortality rate for cardiogenic shock in acute MI remains high when medical therapy alone is used. Percutaneous coronary interventional revascularization procedures such as percutaneous transluminal coronary angioplasty and stenting as well as coronary artery bypass grafting (CABG) are the only interventions that have been shown to improve mortality rates. Mechanical support with percutaneous left ventricular assist devices (LVADs) such as the Tandem Heart and the Impella 2.5 and 5 devices, as well as surgically implanted LVADs, and veno-arterial extracorporeal membrane oxygenation (ECMO) (Chapter 88) are all used in patients with refractory shock despite pharmacologic support and revascularization when appropriate.

DIAGNOSIS

Patients with acute MI may have prolonged anginal pain, dyspnea, diaphoresis, nausea, or emesis (Chapter 50). Because cardiogenic shock usually evolves subsequent to hospitalization, the clinician must be vigilant throughout the patient's hospital course for findings and symptoms that may herald its development. The physical examination may reveal tachycardia, hypotension, tachypnea, and signs of peripheral hypoperfusion (see Figure 8.5), but the lack of these findings does not entirely exclude the development of the shock syndrome. There may be evidence of pulmonary congestion on auscultation of the lungs and either an S_3 or S_4 gallop on cardiac auscultation. A new murmur of mitral regurgitation suggests papillary muscle dysfunction; a precordial thrill suggests a new ventricular septal defect. The ECG signs of acute MI typically include ST segment elevation in multiple leads corresponding to the distribution of the occluded coronary artery, pathologic T waves, and ST segment depression consistent with ischemia in other distributions (Chapter 50). Patients with left main coronary artery disease may have diffuse ST segment depression in all leads, reflecting global ischemia. Lack of distended jugular veins (or a positive hepatic-jugular reflux sign) or elevated CVP (see Figure 8.5) can help to differentiate hypotension caused by drugs or hypovolemia from hypotension resulting from left ventricular dysfunction, right ventricular infarction, tamponade, or a mechanical complication of acute MI.

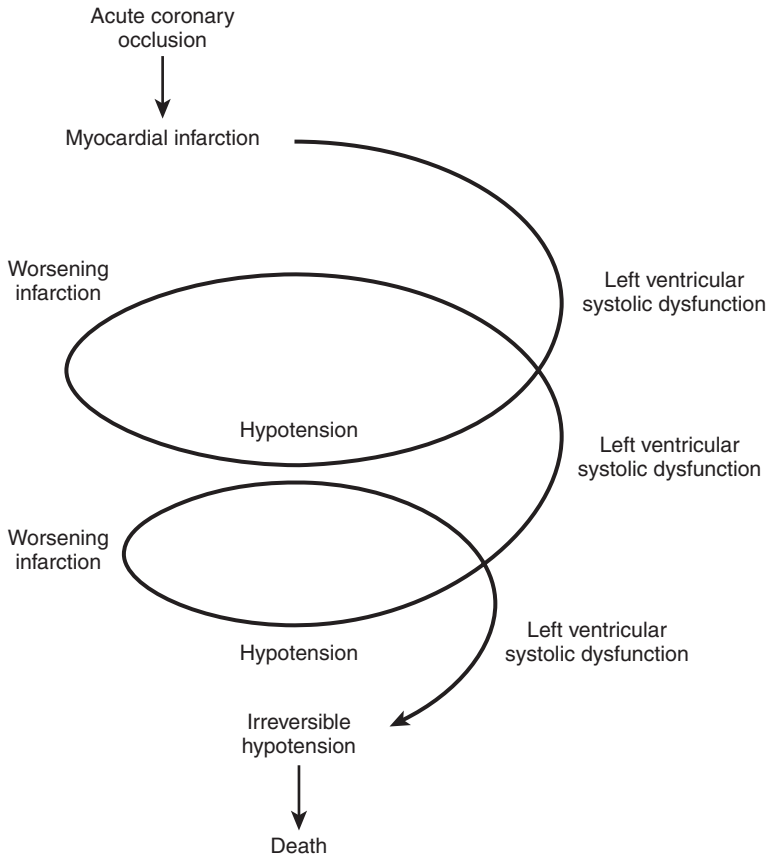


Figure 8.6 Pathophysiologic "death spiral" of cardiogenic shock in acute myocardial infarction with progressive loss of left ventricular function.

A transthoracic echocardiogram (TTE) can distinguish primary left ventricular dysfunction from right ventricular infarction, acute papillary muscle dysfunction with mitral regurgitation, acute ventricular septal defect, or tamponade, and it should be performed early in the course of complicated MI. Preserved left ventricular systolic function by TTE in a patient with cardiogenic shock is an important clue to the presence of a mechanical complication of MI. Transesophageal echocardiography (TEE) is especially helpful in assessing the mechanical complications of acute MI, such as acute papillary muscle rupture or ventricular septal defect, and should be performed if the TTE is not definitive.

GENERAL MANAGEMENT

Early recognition and treatment are essential to the successful management of patients with cardiogenic shock. Two critical principal therapeutic goals are to immediately stabilize the hemodynamic derangement and to restore coronary blood flow. General treatment measures include correcting the hypovolemia, hypoxemia, and acidosis; avoiding or stopping drugs that may produce hypotension or impair cardiac output (e.g., beta-blockers) is imperative. Patients with acute MI should be promptly given aspirin and full-dose intravenous (IV) heparin (Chapter 50).

DRUG THERAPY

Sympathetic Amines

Dopamine, dobutamine, isoproterenol, norepinephrine, and epinephrine have all been used to temporarily improve cardiac performance in patients with cardiogenic shock until more definitive therapy is initiated. Although loosely categorized as beta-agonists, each agent has important differences in the degree of cardiac and peripheral beta-adrenoreceptor effects, alpha-adrenoreceptor effects, and effects on myocardial oxygen consumption and hemodynamics (Tables 8.2 and 8.3). Typically, drugs such as dopamine and norepinephrine are used to provide inotropic and vasopressor support when severe hypotension (e.g., mean arterial pressure < 60 to 65 mm Hg) is present. Because all of these drugs have the potential to increase myocardial oxygen demand and worsen

TABLE 8.2 ■ **Drug Therapy for Cardiogenic Shock**

Drug	Usual Adult Dose Range	Predominant Actions
Sympathomimetic Amines		
Dopamine	3–5 mcg/kg/min	Renal vasodilator
	5–10 mcg/kg/min	Vasodilator and inotrope
	> 10 mcg/kg/min	Vasoconstrictor
Dobutamine	5–20 mcg/kg/min	Inotrope > vasodilator
Isoproterenol	1–10 mcg/kg/min	Chronotropy > inotropy
Epinephrine	1–20 mcg/kg/min	Inotrope, vasodilator
	> 20 mcg/kg/min	Vasoconstrictor
Norepinephrine	1–2 mcg/kg/min	Inotrope
	> 2 mcg/kg/min	Vasoconstrictor
Other Agents		
Milrinone	0.25–0.75 mcg/kg/min	Vasodilator > inotrope
Nitroglycerin	10–50 mcg/kg/min	Venodilator
	50–200 mcg/kg/min	Vasodilator
Nitroprusside	0.5–2 mcg/kg/min	Vasodilator

TABLE 8.3 ■ **Hemodynamic Profiles of Sympathomimetic Amines**

Agent	Inotropy	SVR	CO	HR	$\dot{V}O_2$
Dopamine, low dose	↑	↓	↑	↑	↑
Dopamine, high dose	↑↑	↑↑↑	↑↑	↑↑	↑↑
Dobutamine	↑↑	↓	↑↑	↑↑	↑↑↑
Epinephrine	↑↑	↑↑	↑↑	↑↑↑	↑↑↑
Norepinephrine	↑↑	↑↑↑	↑	↑↑↑	↑
Isoproterenol	↑	↓↓	↑↑	↑↑↑	↑↑↑

SVR, systemic vascular resistance; CO, cardiac output; HR, heart rate; $\dot{V}O_2$, minute oxygen consumption; ↓, decreased; ↓↓, markedly decreased; ↑, mildly increased; ↑↑, moderately increased; ↑↑↑, markedly increased.

myocardial ischemia, they should be used as temporizing measures to maintain adequate hemodynamics while awaiting more definitive therapy.

Vasodilators

Drugs with vasodilator properties such as dobutamine, milrinone, nitroprusside, and nitroglycerin are used to increase cardiac output by reducing afterload (see Figures 8.2 and 8.4) when severe hypotension is *not* present. In patients with systolic arterial blood pressures > 90 mm Hg and low cardiac output, elevated filling pressures, and elevated systemic vascular resistance, the use of vasodilators can also result in decreased pulmonary congestion. Nitroglycerin can reduce ischemia and pulmonary congestion but should only be used when systolic arterial blood pressure is > 100 mm Hg. Profound decreases in systemic arterial pressure that occur after administration of sublingual or IV nitroglycerin and that do not correct with IV volume administration can decrease coronary perfusion and worsen myocardial ischemia. Such episodes should prompt cessation of this drug.

INTRA-AORTIC BALLOON COUNTERPULSATION AND OTHER CIRCULATORY SUPPORT DEVICES

The intra-aortic balloon counterpulsation (IABP) is a removable intra-aortic device that is used to support the circulation. It is placed transfemorally into the descending aorta. It inflates in diastole and, when inflated, blood is displaced into the proximal aorta. Aortic volume, and thus afterload, is reduced during systole through a vacuum effect during rapid balloon deflation. As such, it may be used to reduce left ventricular afterload, reduce myocardial oxygen consumption, increase coronary blood flow, and improve tissue perfusion. Therefore, it has been used in patients with acute MI and cardiogenic shock, as well as a wide variety of other clinical low cardiac output states. It is the most widely used circulatory support device currently available. Prior to the widespread use of thrombolytic therapy or revascularization in acute MI complicated by cardiogenic shock, the use of an IABP was shown to not reduce mortality.

In the era of thrombolytic therapy, there are limited data from randomized trials regarding efficacy of IABP. However, use of an IABP has been shown to be helpful in initial clinical stabilization in a small nonrandomized trial of patients with persistent hypotension and hypoperfusion despite vasopressor therapy. Although more than 70% of these patients had improvement in some parameters of tissue perfusion, their mortality rate remained high (83%). When used together with percutaneous coronary intervention (PCI), nonrandomized observational data from the National Registry of Myocardial Infarction found no reduction in in-hospital mortality associated with IABP use in those undergoing primary PCI for cardiogenic shock, although a

small benefit was found in hospitals with a higher rate of overall IABP use. A meta-analysis in 10,000 patients with cardiogenic shock found no significant benefit with IABP use in the overall cohort, but a significant decrease in 30-day mortality with IABP use in patients treated with fibrinolytic therapy.

Other circulatory support devices, such as left ventricular assist devices (LVADs), are now available from a variety of manufacturers, and their use is increasing. For patients whose cardiogenic shock is refractory to drug therapy, an LVAD can be used to temporarily stabilize a patient or as a bridge to cardiac transplantation (see Chapter 88). Surgically placed left ventricular and biventricular assist devices are typically used as a bridge to transplantation in eligible patients in whom ventricular function is *not* expected to recover. Percutaneous left atrial-to-femoral arterial ventricular assist devices may be used for temporary circulatory support when a surgical LVAD is an option or when recovery of function is uncertain. The Tandem Heart device is placed in the femoral artery (outflow) and via the femoral vein and across the interatrial septum into the left atrium (inflow) via a transseptal catheterization to provide temporary circulatory support while performing high-risk PCI or awaiting ventricular recovery.

Percutaneous transvalvular LVAD systems have become available as well. These devices (Impella 2.5 and the forthcoming Impella 5.0) are placed via the femoral artery, in a retrograde fashion across the aortic valve into the left ventricle. It has a microaxial pump that decompresses the left ventricle and delivers a flow of 2.5 to 5 L/min (depending on device used) into the ascending aorta. Percutaneous cardiopulmonary bypass support with use of extracorporeal membrane oxygenation (ECMO) may also be used for temporary circulatory support when oxygenation is severely impaired as well.

Small randomized trials have evaluated the use of percutaneous LVADs and compared them to IABP therapy in patients with cardiogenic shock following acute MI. One study compared a percutaneous arterial-to-left atrial LVAD (Tandem Heart) to IABP therapy in 41 patients with acute MI and cardiogenic shock. Alteration in the hemodynamic and metabolic parameters associated with shock improved more effectively with the LVAD compared to the IABP, although complications such as significant bleeding and limb ischemia were more common in the LVAD group. Although overall mortality was similar, this study was underpowered to assess this outcome. In a second small study, 25 patients were randomly assigned to an LVAD (Impella 2.5) or an IABP. The LVAD significantly improved hemodynamic parameters such as cardiac output, compared to IABP therapy. Again, outcomes such as death could not be assessed because of the small sample size, but as noted for the Tandem Heart study, mortality rates were similar in the two groups.

REPERFUSION THERAPY WITH THROMBOLYTIC THERAPY

A number of studies have shown that arterial patency is the strongest predictor of survival in patients with acute MI and cardiogenic shock. Although early thrombolytic therapy has been shown to restore arterial patency in the infarcted region, preserve myocardial function, and reduce overall mortality rate in patients with acute MI, it has *not* been shown to appreciably lower mortality rate in patients with cardiogenic shock. In 80 patients with cardiogenic shock in the Italian Group for the Study of Streptokinase in Infarction (GISSI) trial, the mortality rate of patients who received streptokinase was identical to those who did not (70%). In a subgroup analysis of 322 patients with cardiogenic shock from the International Study of Infarct Survival (ISIS), the mortality rate with tissue plasminogen activator (TPA) was 78% and with streptokinase was 65%; both rates were similar to those for historical control subjects. Similarly, in 315 patients with cardiogenic shock in GUSTO I, the mortality rate was 59% for patients given TPA and 55% for those given streptokinase. Whether the addition of intra-aortic balloon pump counterpulsation to thrombolytic therapy improves these outcomes is currently being tested, as noted previously.

REVASCULARIZATION FOR CARDIOGENIC SHOCK

Early revascularization in acute MI, either by percutaneous coronary intervention (PCI) or by CABG, has been shown to restore arterial patency and to improve outcome in cardiogenic shock in nonrandomized studies and newer randomized controlled trials. There are numerous observational and small randomized published studies in those who underwent coronary angioplasty for cardiogenic shock, and those who underwent successful percutaneous coronary intervention (PCI) had lower mortality rates when compared with those with unsuccessful PCI. Similarly, there are numerous studies in those who underwent CABG surgery during hospitalization for acute MI and cardiogenic shock. The in-hospital mortality rate for these pooled patients was 32%, which is the lowest for any treatment modality reported. In a study of more than 200 patients, arterial patency was shown to be the strongest predictor of in-hospital mortality, whether the mechanism was spontaneous, pharmacologic, by PCI, or by CABG.

The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial randomly assigned 302 patients with left ventricular failure following an acute MI to a strategy of emergency revascularization or initial medical stabilization. Emergency revascularization by either coronary artery bypass grafting or angioplasty was required within 6 hours of randomization. Patients assigned to initial medical stabilization could undergo delayed revascularization at a minimum of 54 hours post-randomization. The primary end point of the study was 30-day all-cause mortality. Overall survival at 30 days did not differ significantly between the emergency revascularization and initial medical stabilization groups (53% versus 44%; $P = 0.109$). However, at the 6- and 12-month follow-up, there was a significant survival benefit with early revascularization (50% versus 37%; $P = 0.027$ and 47% versus 34%; $P = 0.025$, respectively). The benefit appeared to be greatest for those < 75 years of age, with 20 lives saved at 6 months per 100 patients treated. In response to the results of the SHOCK trial, the American College of Cardiology/American Heart Association guidelines for acute MI now recommend emergency revascularization for patients younger than 75 years with cardiogenic shock resulting from an acute MI.

IMPAIRED RIGHT VENTRICULAR FUNCTION

Clinically important right ventricular infarction occurs in ~7% of inferior MIs and is associated with a high mortality rate resulting from cardiogenic shock. Right ventricular infarction produces an acute decrease in left ventricular preload, with a resultant decrease in stroke volume and cardiac output. Right-sided filling pressures are typically markedly elevated. The clinical hallmarks of right ventricular infarction are elevated jugular venous pressure, hypotension, and clear lung fields on auscultation. Right-sided primordial leads (V1R to V6R) may reveal ST segment elevation reflecting right ventricular infarction. These changes do not necessarily correlate with hemodynamically significant right ventricular infarction and therefore should be interpreted cautiously. The initial therapy for right ventricular infarction is rapid administration of IV fluids, because high filling pressures (i.e., elevated right atrial and right ventricular pressures) are often required to maintain adequate left ventricular preload and cardiac output. Nitrates should be avoided because they may produce profound hypotension. Pulmonary artery catheterization is often needed for optimization of hemodynamic parameters. Patients who do not respond to volume administration should be supported with inotropes such as dobutamine or milrinone if severe hypotension is not present. Drugs that increase pulmonary vascular resistance (e.g., dopamine, norepinephrine) and therefore worsen right ventricular function should be avoided if possible. As stated earlier, prompt revascularization with either PTCA or CABG should be performed as indicated.

ACUTE MECHANICAL COMPLICATIONS OF MI

Acute mechanical complications of MI may also result in cardiogenic shock. Papillary muscle infarction or rupture may cause acute severe mitral regurgitation. Acute ventricular septal rupture produces a left-to-right shunt with acute right-sided volume overload and an inadequate left-sided cardiac output. Physical examination of patients with papillary muscle dysfunction or rupture often reveals a holosystolic murmur of mitral regurgitation. Those with a ventricular septal defect often have a harsh systolic murmur, with an accompanying thrill across the precordium. Physical examination findings, however, may be nonspecific or even absent in patients with either complication.

TTE or TEE is particularly helpful in identifying acute mechanical complications of MI from primary pump failure caused solely by left ventricular dysfunction. Preserved, normal, or hyperdynamic left ventricular function found on TTE in a patient with shock can be an important clue to an underlying mechanical complication and should prompt consideration of TEE if the diagnosis is not clear. Flow-directed pulmonary artery catheterization can also help differentiate severe mitral regurgitation and ventricular septal rupture from intrinsic left ventricular dysfunction (see Table 8.1). Patients with severe mitral regurgitation may have large V waves in the pulmonary artery wedge tracings, although this finding is neither sensitive nor specific for mitral regurgitation. Large V waves can also be seen in acute ventricular septal rupture as a result of the increased volume load presented to the left atrium.

Patients with acute ventricular septal rupture or mitral regurgitation and cardiogenic shock pose difficult management problems because they often benefit from afterload reduction with vasodilator drugs, but they can be profoundly hypotensive. Often, an empirical trial of low-dose vasodilators is warranted. If worsening hypotension ensues, then intra-aortic balloon counterpulsation should be considered. Definitive therapy with either surgical repair of the ventricular septal defect or replacement of the mitral valve should be undertaken promptly because the mortality of patients who receive medical therapy alone is extremely high. The use of concomitant revascularization is controversial, but there are trends favoring improved survival rate in those who undergo ventricular septal defect repair or mitral valve replacement with CABG. The condition of some patients with acute mechanical complications of MI may be too tenuous for them to undergo concomitant revascularization, being unable to tolerate prolonged cardiopulmonary bypass. Despite corrective surgery, mortality rates are high.

Other Causes of Cardiogenic Shock

DISTURBANCES OF CARDIAC RHYTHM

Severe tachyarrhythmias or bradyarrhythmias can acutely disrupt cardiac output and result in cardiogenic shock, because heart rate is an important determinant of cardiac output and ventricular filling. Rapid supraventricular or ventricular tachycardia may be associated with marked reductions in diastolic filling time and ventricular stroke volume. Supraventricular tachycardia, such as atrioventricular (AV) nodal reentrant tachycardia (Chapter 34), may also be associated with simultaneous atrial and ventricular contraction, which further reduces ventricular filling. Even patients with normal ventricular function often poorly tolerate heart rates of more than 200 beats per minute. Abnormal ventricular systolic function or diastolic dysfunction makes it much more likely that rapid heart rates will result in hemodynamic instability. Patients with rapid tachyarrhythmias of any origin who are hemodynamically unstable should be urgently cardioverted to restore sinus rhythm (see Chapter 34 and Advanced Cardiovascular Life Support [ACLS] algorithms in Appendix E).

Similarly, severe bradycardia or high-grade heart block may acutely reduce cardiac output and result in hemodynamic instability. Reduced diastolic filling may also occur as a result of

asynchronous atrial and ventricular contractions, and further reduce cardiac output. Prompt treatment with transcutaneous or transvenous pacing is necessary to improve cardiac output and acutely altered hemodynamics (see Chapter 33).

ACUTE MYOCARDITIS AND CARDIOMYOPATHY

Acute myocarditis can also produce cardiogenic shock through a loss of intrinsic myocardial pump function. Giant cell myocarditis, in particular, is associated with a fulminant course and rapid hemodynamic deterioration. Although certain subsets of patients may benefit from immunosuppressive therapy, no specific therapy has been shown to definitively alter mortality rates in these patients; therefore, the treatment remains supportive.

Progressive heart failure from cardiomyopathy of any cause can also result in cardiogenic shock (Chapter 52). Chemotherapeutic agents such as doxorubicin can cause an acute toxic cardiomyopathy and result in cardiogenic shock.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 9

Hemorrhagic Shock

Daniel N. Holena ■ Vicente H. Gracias

When global tissue perfusion is inadequate to meet the body's metabolic demand, a state of shock exists. Conceptually, shock can be divided into three distinct but overlapping categories: cardiogenic shock, distributive shock, and hypovolemic shock. Although the late stages of shock are easily recognized by the presence of tachycardia and hypotension, its presentation may be insidious and manifest only as multiple end organ dysfunction secondary to hypoperfusion. Furthermore, because individual organs may be variably affected, a patient with only subtle hemodynamic perturbations may present with nonspecific signs, such as oliguria, skin pallor, coolness of extremities, and altered mental status.

Cardiogenic shock (see Chapter 8) results from an inability of the heart to effectively pump blood to surrounding tissues. Compensatory activation of the sympathetic nervous system increases systemic vascular resistance in an attempt to restore perfusion pressure that in some patients is manifested by cool extremities with a netlike pattern of bluish skin mottling known as *livedo reticularis*.

Distributive shock (Chapter 10) is characterized by a loss of vasomotor tone in capacitance and resistance vessels. Therefore, circulating blood volume is effectively insufficient ("relative hypovolemia"). In addition, it results in a low afterload state as a result of low systemic vascular resistance.

Hypovolemic shock results from a decrease in actual intravascular volume, the etiology of which may be myriad (Box 9.1). Hemorrhagic shock, the most common form of hypovolemic shock, is classically divided into four stages of severity (Table 9.1). These four stages correspond to the progression of blood loss and the associated physiologic responses in otherwise healthy individuals with normal cardiopulmonary systems.

Although conceptually useful, the distinction between cardiogenic, distributive, and hypovolemic shock is somewhat artificial as shock is frequently multifactorial. For instance, a patient who has sustained severe thermal burns will almost certainly manifest hypovolemia as intravascular volume migrates into the interstitial space secondary to capillary leak. The same patient may also have attenuated vasomotor tone secondary to the systemic inflammatory response syndrome (SIRS; see Chapter 10) causing a distributive shock. Finally, a fraction of patients with distributive shock caused by sepsis may also have an element of cardiogenic shock resulting from the depression of myocardial function from circulating inflammatory mediators or from preexisting disease or other factors.

Pathophysiology of Decreased Preload

Cardiac output is the product of heart rate and stroke volume. Stroke volume, in turn, is determined by ventricular preload, contractility, and afterload (Figures 8.1-8.4, Chapter 8). Preload corresponds to the stretch placed on cardiac muscle immediately prior to contraction. There is a direct relationship between sarcomere length (or stretch) and contractile force. As illustrated by

BOX 9.1 ■ Causes of Shock Resulting from Hypovolemia or Decreased Venous Return

Decreased Intravascular Volume

- Hemorrhage
- Gastrointestinal tract losses
  - — Vomiting or elevated nasogastric tube outputs
  - — Diarrhea
  - — Enterocutaneous fistula
- Renal losses
  - — Polyuria in diabetic ketoacidosis
  - — Postobstructive diuresis
  - — Neurogenic diabetes insipidus in head trauma
- Inflammatory "third spacing": extravasation of intravascular volume into the interstitium
  - — Pancreatitis
  - — Thermal or chemical burns
  - — Abdominal surgery

Decreased Venous Return to the Heart*

- Abdominal compartment syndrome (Chapters 90 and 97)
- Elevated intrathoracic pressures
  - — Tension pneumothorax
  - — Positive pressure ventilation
  - — Excessive positive end-expiratory pressure (PEEP) or auto-PEEP (Chapter 2)
- Cardiac (pericardial) tamponade (Chapter 54)
- Venodilation
- Anaphylaxis
- Cervical spinal cord injuries
- Spinal and epidural anesthesia

**With normal global blood volume.*

the Starling curves, increasing preload increases the force of muscle fiber contraction and cardiac stroke volume up to a maximum after which the output plateaus (see Figure 8.1). The term *preload* is most accurately reflected by left ventricular end-diastolic volume (LVEDV) rather than the left ventricular end-diastolic pressure (LVEDP), which is commonly estimated in the intensive care unit (ICU) using the pulmonary artery catheter. For clinical purposes, the LVEDP is often assumed to be proportional to the LVEDV, although this relationship may become nonlinear, particularly in the noncompliant myocardium because of preexisting diastolic dysfunction (such as that caused by chronic hypertension) or ischemia. Preload is a function of the global circulating blood volume as well as venous return to the heart (see Box 9.1).

PHYSIOLOGIC AND PATHOPHYSIOLOGIC CHANGES IN HYPOVOLEMIC SHOCK

Hypovolemic shock is characterized by a decreased cardiac preload, which results in a decreased stroke volume. Compensatory mechanisms for low cardiac output or hypotension are mediated by means of a sympathetic adrenergic response. In an attempt to maintain cardiac output, the force of cardiac contraction (inotropy) and the rate of contractility (chronotropy) both increase (see Figure 8.2). As hypovolemia progresses, in an effort to maintain an adequate perfusion pressure to organs, systemic vascular resistance and left ventricular afterload increase, redirecting blood flow

TABLE 9.1 ■ **Estimated Blood Loss Based on Patient's Initial Presentation**

Parameter	Class I	Class II	Class III	Class IV
Blood loss (mL)*	Up to 750	750–1500	1500–2000	> 2000
Blood loss (% blood volume)	Up to 15%	15–30%	30–40%	> 40%
Pulse rate	< 100	100–120	120–140	> 140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mm Hg)	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate	14–20	20–30	30–40	> 35
Urine output (mL/h)	> 30	20–30	5–15	Negligible
CNS/mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Fluid replacement	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood

*Values are based on an adult with a predicted body weight (PBW) of 70 kg in which total intravascular blood volume is estimated at 70 mL per kg PBW or, in this example, 70 mL x 70 kg PBW = 4900 mL or ~5000 mL.

The guidelines in this table are based on the 3-for-1 (3:1) rule, which derives from the empiric observation that most patients in hemorrhagic shock require as much as 300 mL of electrolyte solution for each 100 mL blood loss. Applied blindly, these guidelines may result in excessive or inadequate fluid administration. For example, a patient with a crush injury to an extremity may have hypotension that is out of proportion to his or her blood loss and may require fluids in excess of the 3:1 guidelines. In contrast, a patient whose ongoing blood loss is being replaced by blood transfusion requires less than 3:1. The use of bolus therapy with careful monitoring of the patient's response may moderate these extremes.

From American College of Surgeons: Advanced Trauma Life Support Student Course Manual, 8th Ed. Chicago: American College of Surgeons, 2008, with permission.

from the periphery (skin, skeletal muscles, and fat in extremities) and from the splanchnic bed to the central circulation. For example, blood flow to the kidneys may decrease to only 5% to 10% of normal during acute hypovolemia, supporting the utility of monitoring urine output per hour as a gauge of adequate renal blood flow.

During hypovolemic shock the venous capacitance beds constrict as well, enhancing blood return to the heart. The renin-angiotensin system is activated, causing a release of aldosterone from the adrenal cortex and arginine vasopressin (antidiuretic hormone) from the posterior pituitary. These enhance renal reabsorption of sodium and water, which act to preserve the circulating blood volume. In addition to its antidiuretic effects, arginine vasopressin is a potent vasoconstrictor. Other endocrine responses include increased levels of plasma glucagon, cortisol, and growth hormone. Along with an increase in endogenous catecholamine release, these hormones all tend to increase the plasma glucose level.

Blood pressure within vascular beds influences microcirculatory flow, which is further regulated by precapillary and postcapillary sphincters. Sphincter tone is controlled by autoregulation of the capillary bed and by the autonomic nervous system. The former is mediated both by endothelial stretch receptors, which modulate microcirculatory tone at varying perfusion pressures, and by the concentration of various metabolites mediating local vasodilatation (e.g., nitric oxide). In contrast, the sympathetic nervous system primarily results in vasoconstriction through an increase in precapillary tone. In the early phases of shock, this may serve to shunt blood away from the skin and skeletal muscle toward organs necessary for immediate survival.

When all these compensatory mechanisms are active, the patient may tolerate even severe fluid loss with minimal or no tissue dysfunction ("compensated shock") or with some reversible tissue

BOX 9.2 ■ Basic Equations Related to Oxygen Delivery and Uptake

Equation 1: Arterial Oxygen Content

$Cao_2 = [Hgb \times 1.39\ mL\ O_2/g] \times Sao_2 + [Pao_2 mm \times 0.0031\ mL\ O_2/mm\ Hg/dL]$
where Cao_2 = oxygen content of arterial blood (mL/dL)
Hgb = hemoglobin concentration (g/dL)
Sao_2 = oxygen saturation of hemoglobin in arterial blood

Equation 2: Oxygen Delivery

$\dot{D}o_2 = Cao_2 \times CO$
$\dot{D}o_2$ = oxygen delivery (mL O_2/min)

Equation 3: Oxygen Consumption

$\dot{V}o_2 = [Cao_2 - C\bar{v}o_2] \times CO$
where $\dot{V}o_2$ = minute oxygen consumption (mL/min)
$C\bar{v}o_2$ = oxygen content of mixed venous blood (mL/dL)

Equation 4: Oxygen Extraction Ratio (ER)

$ER = \dot{V}o_2/\dot{D}o_2 = [Cao_2 - C\bar{v}o_2]/Cao_2 = [Sao_2 - S\bar{v}o_2]/Sao_2$
where ER = oxygen extraction ratio
Sao_2 = O_2 saturation of arterial blood
$S\dot{V}o_2$ = O_2 saturation of mixed venous blood*

**Mixed venous blood is obtained from the pulmonary artery.*

dysfunction ("progressive shock"). In these states, resuscitation alone will restore the intravascular volume and is likely to reverse inadequate tissue perfusion. As both the volume of blood lost and length of time in shock increase, the degree of reversibility in response to intravascular volume resuscitation decreases and eventually it reaches an irreversible state in which survival is unlikely.

From a macrocirculatory standpoint, circulatory shock can be described as an imbalance between tissue oxygen supply and demand. Systemic oxygen delivery ($\dot{D}o_2$) is equal to the product of arterial oxygen content and cardiac output (Box 9.2). Oxygen consumption per minute ($\dot{V}o_2$) is dependent on the body's total metabolic activity, distribution of blood flow, and the ability of tissues to extract and utilize oxygen. The mixed venous oxygen saturation ($S\bar{v}o_2$) is measured in the pulmonary artery and is dependent on the relationship between $\dot{D}o_2$ and $\dot{V}o_2$. The oxygen extraction ratio ($\dot{V}o_2/\dot{D}o_2$) represents the proportion of delivered oxygen to the oxygen consumed by the tissues. Under normal conditions, the $\dot{V}o_2/\dot{D}o_2$ is approximately 1/4, which corresponds to an $S\bar{v}o_2$ of ~75%. Under normal conditions, the amount of oxygen delivered to the tissues ($\dot{D}o_2$) is far in excess of oxygen consumption ($\dot{V}o_2$), and this explains why $\dot{V}o_2$ typically varies independent of $\dot{D}o_2$ (Figure 9.1).

When oxygen delivery becomes inadequate to match the tissue requirements (i.e., oxygen consumption), the tissues affected begin to utilize anaerobic metabolism to generate adenosine triphosphate (see Figure 9.1). Under these conditions, increases in $\dot{D}o_2$ can increase $\dot{V}o_2$, or, expressed in another way, $\dot{V}o_2$ becomes *dependent* on $\dot{D}o_2$ ("$\dot{D}o_2$ dependent" or "supply dependent"). As a result of inadequate oxygen delivery and conversion of cells from an aerobic environment to anaerobic, lactic acid ("lactate") is generated. If this imbalance is not corrected, cell death is inevitable. In uncomplicated forms of low-output shock, which is isolated hypovolemic or cardiogenic shock, restoration of $\dot{D}o_2$ alone will reverse the pathologic process. However, in septic shock, whether $\dot{V}o_2$ is $\dot{D}o_2$ dependent when cardiac output is normal or even supranormal remains controversial. As in low-output shock, tissue ischemia and elevated lactic acid production can also be seen with septic shock, but this is often accompanied by a high $\dot{D}o_2$ and normal or

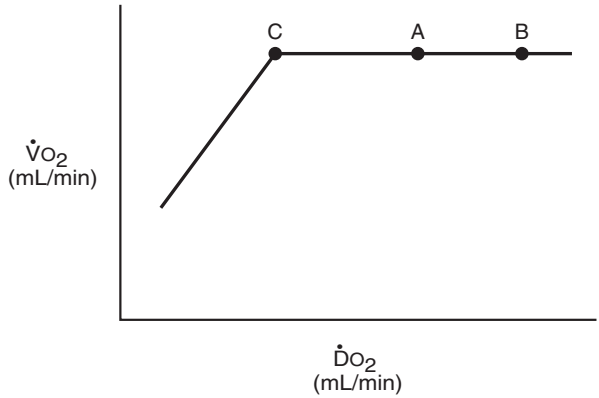


Figure 9.1 Schematic two-phase model illustrating the relationship between oxygen delivery to the whole body ($\dot{D}o_2$) and whole-body minute oxygen consumption ($\dot{V}o_2$) under normal (non–critically ill) conditions. At point A, representing a normal resting value for $\dot{D}o_2$ (e.g., when the oxygen extraction ratio, $\dot{V}o_2/\dot{D}o_2$, is 0.3, Equation 4, Table 9.3). If $\dot{D}o_2$ is increased to point B (e.g., by increasing heart rate by pacing or by transfusion), $\dot{V}o_2$ remains unchanged. In this case, $\dot{V}o_2$ is *independent* of increases in $\dot{D}o_2$ because O_2 delivery is already in excess of O_2 consumption. If $\dot{D}o_2$ *decreases* from point A, $\dot{V}o_2$ also remains unchanged (owing to increased extraction of O_2 from the blood by metabolizing tissues—i.e., increased $\dot{V}o_2/\dot{D}o_2$) until $\dot{D}o_2$ reaches a critical value ($\dot{D}o_2c$), at point C. Below point C, $\dot{D}o_2$ is no longer adequate to satisfy whole-body O_2 demand and, because oxygen extraction is maximal at this point, further decreases in $\dot{D}o_2$ result in decreases in $\dot{V}o_2$. Under these circumstances, $\dot{V}o_2$ is *dependent* on $\dot{D}o_2$.

supranormal $S\bar{v}o_2$ (≥70%) (see Box 9.2, Equation 4). Thus, one should not expect an increase in $\dot{D}o_2$ to correct the derangements in microcirculatory blood flow or the abnormalities in oxygen extraction or utilization in septic shock. Indeed, prospective randomized clinical trials to date have not supported the efficacy of increasing global $\dot{D}o_2$ in the treatment of septic shock (see Chapter 10).

With the progression of shock, volume replacement alone becomes an ineffective treatment modality. Severe hemorrhagic shock triggers a series of events at the cellular and molecular level, which teleologically are thought to be adaptive responses designed to help the organism survive the initial insult. As shock progresses, these mechanisms are amplified to the point where they are no longer controlled and cease to be adaptive. In hypovolemic shock, as in septic shock, the inflammatory cascade is activated, causing release of multiple proinflammatory cytokines, such as tumor necrosis factor-alpha, interleukin-1, and interleukin-6. The clinical manifestation of this process is termed the *systemic inflammatory response syndrome* (SIRS). The proinflammatory mediators contribute to tissue injury, including programmed cell death (apoptosis) and organ failure by themselves. Furthermore, their effect on the vasculature tends to promote capillary leak, exacerbating intravascular hypovolemia and causing anasarca, which may be marked during volume resuscitation.

The role that genetics play in an organism's response to shock is being actively investigated. Studies in rat models of hemorrhagic shock suggest significant interstrain variability in survival. Further research is required before novel therapeutic approaches can be translated into clinical care.

Clinical Manifestations

Hypovolemic shock is often, but not always, apparent on physical examination. When present, the skin may be pallid, cool, and clammy; *livedo reticularis* (mottling of the skin representing cutaneous vascular insufficiency) may be present over the extremities. The feet and hands are typically

cooler than the torso, and capillary refill may exceed 2 seconds. Skin turgor may decrease when hypovolemia is subacute or chronic. Cerebral hypoperfusion may result in a spectrum of altered mental status ranging from anxiety in the earliest stages of shock to frank obtundation in the later stages. Classically, the first change in hemodynamic parameters caused by low preload shock is a decrease in pulse pressure; however, this finding may be difficult to appreciate in a patient's initial presentation without knowledge of baseline pulse pressure. As intravascular volume decreases, compensatory tachycardia typically follows in an attempt to maintain cardiac output. Sympathetic output increases vascular tone, though blood pressure may remain in the normal range. As intravascular volume continues to decline, these compensatory mechanisms are overwhelmed and hypotension develops. Oliguria may also be seen as shock progresses, partly because of renal hypoperfusion as well as the effects of aldosterone. It is important to recognize that the absence of tachycardia and hypotension does not exclude the presence of shock; occult shock can occur in patients with "stable" vital signs. In particular, the hypertensive elderly patient on beta adrenoreceptor blockers may have a blunted tachycardic response to intravascular volume loss. A "normal" systolic blood pressure may in fact be much lower than a patient's baseline blood pressure and be inadequate for tissue perfusion. Additionally, young, well-conditioned patients may be relatively bradycardic at baseline; a compensatory increase in heart rate in this population may still fall within the norms of the general populace. A decrease in preload may be compensated for by intense vasoconstriction, leading to relatively normal hemodynamic indices until all reserve is exhausted and cardiovascular collapse ensues.

Clinical Management

The initial management of shock is dictated by well-established priorities as delineated by Advanced Cardiac Life Support (ACLS) protocols: the ABC's of resuscitation. The airway (A) should be assessed and, if not secure, the patient should be endotracheally intubated. Adequate ventilation and oxygenation (breathing, B) should be ensured. To restore circulation (C), large-bore peripheral intravenous access should be immediately established and sources of hemorrhage controlled. The shorter length and larger diameter of large-bore peripheral IVs allow for higher rates of infusion, making them preferable to many central venous lines for the purposes of resuscitation (see Chapter 11). Resuscitation is typically initiated with isotonic crystalloid solutions (usually lactated Ringer's solution or normal saline) while the underlying cause of shock is being identified. Visible external hemorrhage is best controlled with direct pressure where possible. If hemorrhage is known to be the cause of hypotension and immediate control cannot be obtained, initiation of uncrossmatched blood transfusion is appropriate. Much research has been conducted on the optimal fluid of resuscitation for hypovolemic shock, but it can be summed up as follows: isotonic crystalloids available for resuscitation appear to be essentially equivalent and colloid resuscitation has not been shown to be superior to crystalloid resuscitation. Fluid and blood product administration should be tailored according to the appropriate clinical situation (see Chapter 19).

In the case of suspected hypovolemic shock, heart rate and cardiac rhythm should be closely followed. Serial blood pressure determinations should be obtained manually, with an automatic blood pressure cuff or, ideally in an unstable patient, with an indwelling arterial catheter. A urinary drainage catheter should be placed to accurately monitor urine output.

In hemorrhagic shock, Advanced Trauma Life Support (ATLS) guidelines recommend the initiation of packed red blood cell (PRBC) transfusion if the patient's vital signs do not stabilize after rapid intravenous infusion of 2 L of lactated Ringer's solution (Chapter 95). However, in the case of hemorrhage without source control, crystalloid resuscitation should be minimized and blood transfusion initiated immediately. However, there may be benefit in so-called hypotensive resuscitation in patients who have uncontrolled sources of bleeding. In this paradigm, relative

hypotension is permitted until definitive control of bleeding is obtained. Several studies have investigated this hypothesis, but no definitive improvement in mortality has been demonstrated.

Currently, no substitutes for human blood or blood components have been proven to be safe and efficacious. Therefore, the treatment of exsanguinating hemorrhage necessitates the use of human blood products, specifically packed red blood cells (PRBCs). Restoration of circulating volume with PRBCs alone can exacerbate the coagulopathy seen in hemorrhagic shock and is to be avoided. Current hemostatic resuscitation guidelines dictate that PRBCs and fresh frozen plasma (FFP) should be transfused in a 1:1 or 1:2 ratio in an attempt to reapproximate the characteristics of the whole blood that is shed.

Patients with a presumptive diagnosis of hypovolemic shock who fail to respond to empiric volume replacement represent a vexing problem. If the underlying cause of the shock state is not easily discernible or rapidly correctable, or if the patient fails to respond as expected to therapy, more sophisticated evaluation of the patient's hemodynamics must be considered. Traditionally, attempts to estimate volume responsiveness have relied on placement of central venous catheters (CVCs) or pulmonary artery catheters (PACs). With CVC placement, central venous pressure is used as an estimate of right ventricular end-diastolic pressure and thus as a surrogate for right heart preload. The PAC can be used to measure the pulmonary arterial wedge pressure, which (assuming correct catheter placement and no valvular disease) should be roughly equivalent to left ventricular end-diastolic pressure. This pressure is used to estimate left ventricular end-diastolic volume, which is considered to be a surrogate for left heart preload. In addition, the PAC allows for estimation of cardiac output and can be used to measure mixed-venous oxygen saturation (see Chapters 7 and 11). The notion of using CVC and PAC pressures as surrogates for cardiac preload can be problematic and relies on many assumptions about ventricular compliance, cardiac valve function, proper positioning, and operator proficiency. For volume administration to be effective, both the right and the left heart must be on the underfilled portion of the Starling curve, a phenomenon known as biventricular preload responsiveness. These difficulties have prompted investigation into alternate methods of determining volume responsiveness. Among the most promising are those that examine pulse pressure variation throughout the respiratory cycle in patients with indwelling arterial pressure lines. In extubated patients, the intrathoracic pressure can be elevated by asking patients to do a Valsalva maneuver (a sustained forced expiration against a closed glottis); a reduction in pulse pressure with this maneuver has been shown to predict volume responsiveness. In intubated, paralyzed patients receiving positive pressure ventilation, a reduction in pulse pressure during delivery of a mechanical breath can accurately be used to determine volume responsiveness. Many variations on these themes are currently in publication and new technology specifically targeted at measuring pulse pressure variation on a continuous basis may provide a more accurate assessment of biventricular preload responsiveness than traditional methods.

The adverse effects of over-resuscitation include congestive heart failure, respiratory failure, increased ventilator days, and wound and soft tissue complications. Of particular concern in patients being aggressively resuscitated during abdominal surgery is the formation of bowel and abdominal wall edema; this may preclude fascial closure necessitating going to the ICU with an "open abdomen." If the fascia has already been closed, ongoing resuscitation may precipitate abdominal compartment syndrome (see Chapters 90 and 97). Thus, the goal is to resuscitate the patient "enough" to prevent progressive organ dysfunction but not "too much" to precipitate downstream complications of excessive volume replacement. This then raises the following questions: How much is enough, and how much is too much? Titration of resuscitation to the clearance of biochemical markers, such as lactate and base deficit, has been posited as a method for monitoring and addressing subclinical hypoperfusion. As such, these markers of "metabolic debris" can be followed serially in patients after hemorrhagic shock. Normalization of lactate in the patient with traumatic shock portends a more favorable long-term prognosis and thus is often

used as an end point of resuscitation. However, as with any laboratory tests, aberrant lactate or base deficit values must be taken in clinical context. Lactate may be elevated in many nonhypoperfused states, including seizure activity, diabetic ketoacidosis, and as a result of some medications (Chapters 82 and 83). Likewise, a base deficit may be present secondary to renal dysfunction, chronic obstructive pulmonary disorder (COPD), hyperchloremia, or any other situation resulting in an acidemia and thus may not necessarily represent hypoperfusion.

After the control of severe hemorrhage, volume administration, vasopressors, and inotropes can sometimes be used to restore acceptable hemodynamic parameters. In some patients, however, this response will be transient and shock will progress to a state of multiorgan failure and ultimately death. This underscores the point that, in the advanced stages of hemorrhagic shock, it is not sufficient to simply restore intravascular volume with blood component therapy. The progression of global hypoperfusion to a state of irreversible shock depends on the degree of blood lost and the time spent in shock and is primarily mediated at the cellular and molecular level.

Investigation is ongoing to discover treatment modalities that are targeted toward preventing the progression of shock into an irreversible state. Currently, however, care in the latter stages of shock continues to be supportive.

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CHAPTER 10

Septic Shock

Mark E. Mikkelsen ■ Barry D. Fuchs

Sepsis is a life-threatening condition that requires early recognition and aggressive management by critical care practitioners. In the United States alone, approximately 750,000 individuals develop sepsis annually, more than 200,000 of whom will die. The sixth leading cause of death in the United States, sepsis accounts for nearly 20% of all intensive care unit (ICU) admissions and $17 billion in annual costs.

Clinical Considerations

DEFINITIONS AND CLINICAL MANIFESTATIONS

The clinical manifestations of sepsis include the local symptoms and signs of the inciting infection as well as systemic signs, which are manifestations of the body's response to the infection. Although the clinical features of the infection are relatively specific to the anatomic site, the systemic response is not. The systemic response, formally called the *systemic inflammatory response syndrome* (SIRS), includes both vital sign (fever, tachycardia, and tachypnea) and laboratory (leukocytosis or leukopenia) abnormalities (Table 10.1).

Consider sepsis severe when associated with hypoperfusion, organ dysfunction, or hypotension. Criteria for organ dysfunction have been specified (see Table 10.1). Septic shock is defined as refractory hypotension despite an adequate intravenous fluid volume challenge (> 20 to 30 mL/kg of crystalloid, or approximately 1 to 1.5 L). This categorization is important clinically, as it informs both triage and therapeutic decisions and has prognostic value.

PATHOPHYSIOLOGY

The severity of an infection depends on both the pathogen's virulence and the body's pathophysiologic response to the infection. The Toll-like receptor (TLR) family plays an important and proximal role in both pathogen recognition (innate immunity) and initiation of the hosts' inflammatory response. TLR-2 recognizes peptidoglycan in the cell wall of gram-positive pathogens; TLR-4 detects lipopolysaccharide in the outer membrane of gram-negative pathogens. This family of receptors also recognizes viral and fungal pathogens.

TLRs also play an integral role in the initiation of the "cytokine storm" of sepsis. These inflammatory cytokines stimulate neutrophils and endothelial cells, including the activation of procoagulant pathways. This adaptive immune reaction, through a complex, interactive relationship, augments innate immune activation to enable a more effective response to the infection. Simultaneously activated biologic pathways down-regulate and control this response; however, the host's immune response may become maladaptive, resulting in organ dysfunction, circulatory shock, and death. The specific mechanisms that regulate this response, and the genetics underlying their control, currently represent intense areas of investigation. Although the multifactorial pathophysiology of organ dysfunction extends beyond the scope of this chapter, circulatory shock

TABLE 10.1 ■ **International Consensus Definitions of SIRS, Sepsis, Severe Sepsis, and Septic Shock**

Term	Criteria
SIRS	Presence of ≥ 2 of 4 of the following signs* of systemic inflammation:
	Temperature (> 39° C or 101.5° F or < 36° C or 94° F)
	Tachycardia (> 90 beats per minute)
	Tachypnea (> 20 breaths per minute or $PaCO_2$ < 32 mm Hg)
	Abnormal white blood cell count (> 12,000 cells/μL or < 4000 cells/μL) or > 10% bandemia
Sepsis	SIRS *plus* known or suspected infection
Severe sepsis	Sepsis *plus* evidence of hypoperfusion, hypotension, or organ dysfunction:*
	1. Hypoperfusion (serum lactate measurement > 3 mmol/L)
	2. Hypotension (systolic blood pressure < 90 mm Hg or > 40 mm Hg fall from baseline in patients with hypertension; mean arterial pressure < 60 mm Hg)
	3. Central nervous system failure (change in mental status defined as a decrease of 2 points on Glasgow Coma Scale)
	4. Coagulation failure (INR > 1.5 or aPTT > 60)
	5. Hematologic failure (platelets < 100,000/μL)
	6. Gastrointestinal failure (ileus)
	7. Hepatic failure (total bilirubin > 4 mg/dL)
	8. Renal failure (oliguria defined as a urine output < 0.5 mL/kg/h or creatinine increase ≥ 0.5 mg/dL)
	9. Respiratory failure (Pao_2/Fio_2 < 300)
Septic shock	Severe sepsis *plus* fluid-refractory hypotension

*Without alternative explanation.
SIRS, systemic inflammatory response syndrome; INR, international normalized ratio; aPTT, activated partial thromboplastin time; criteria values are those recommended by the 2001 International Sepsis Definitions Conference.

plays a central role. Shock is an important and early clinical manifestation of severe sepsis, and treatment of shock may be lifesaving. Therefore, it is important to understand the pathophysiology and hemodynamics of septic shock.

Activated neutrophils release mediators, which increase microvasculature permeability. This leads to third spacing and further exacerbates the decrease in intravascular fluid volume typically present on admission because of anorexia and external fluid losses (sweating, gastrointestinal, etc.). In addition, activated endothelial cells induce nitric oxide production, which leads to widespread vasodilatation (low systemic vascular resistance) impairing the compensatory response to hypovolemia. Furthermore, in up to 60% of patients with septic shock, a sepsis-induced cardiomyopathy (SIC) contributes to the circulatory derangements. Serum troponin levels are a sensitive marker of SIC and proportional to both the severity of cardiac dysfunction and patient prognosis. However, the underlying pathophysiology does not involve coronary ischemia or infarction.

Importantly, although widespread vasodilation (and low afterload) is a central feature of septic shock, the physical exam findings characteristic of a high cardiac output state (i.e., "warm shock") are often absent on initial presentation. Rather, septic patients commonly present with findings consistent with a low cardiac output (i.e., "cold shock"), exhibiting a narrow pulse pressure, cool extremities, and mottled skin. This apparent paradox can be reconciled by dismissing the notion that vasodilation directly allows a reflex increase in cardiac output. A cardiac output rise in response to systemic vasodilation requires sufficient driving pressure (i.e., the mean systemic

BOX 10.1 ■ Differential Diagnosis of Low Afterload Shock

Anaphylaxis (see Chapter 32)
Central nervous system disorders, including stroke, dysautonomias, and spinal shock (see Chapters 67 and 101)
Diffuse erythroderma (see Chapter 43)
Drug overdoses (see Chapter 57)
Effects of anesthetics (see Chapter 87)
Endocrine emergencies, including myxedema coma and addisonian crisis (see Chapter 85)
Hyperthermia, including neuroleptic malignant syndrome (see Chapter 55)
Sepsis
Transfusion reactions (see Chapter 46)

pressure; Pms) to the venous system to allow an increase in venous return, as cardiac output must equal venous return. Pms, as determined by the venous blood volume and compliance of the venous blood vessels, is often decreased on patient presentation because of profound hypovolemia and sepsis-induced venodilation (which increases venous compliance), respectively. Furthermore, SIC, present in many patients, further contributes to the impairment in cardiac output. This pathophysiology can lead to the findings of poor extremity perfusion on admission, as well as a low central venous pressure (CVP) and central venous oxygen saturation ($ScvO_2$).

Nevertheless, after repletion of intravascular volume, which may require up to 7 to 9 L in the first 24 hours, the classic findings of warm shock become manifest in most patients, including a wide pulse pressure and warm, well-perfused, extremities. This adaptive response to volume repletion occurs in most patients and is essential for survival. Even with SIC, an increase in end diastolic volume (preload) as a result of ventricular dilatation compensates for the reduction in inotropy, along with decreased afterload from arterial vasodilatation.

DIFFERENTIAL DIAGNOSIS

A limited set of disorders can mimic the warm shock (low afterload) state characteristic of well-resuscitated septic shock (Box 10.1); however, in those patients presenting in cold shock, one must consider a broader differential including disorders associated with a low cardiac output and high afterload. This broader differential includes all the other categories of shock including hypovolemic, cardiogenic, and obstructive. Although this includes a long list of disorders, initial findings on history and physical exam (e.g., clinical setting and absence of jugular venous distention and rales) usually allow one to readily exclude cardiogenic and obstructive shock from initial consideration.

Clinical Management of Septic Shock

RECOGNITION

It is vitally important to recognize sepsis promptly, particularly when severe, as delays will reduce the effectiveness of lifesaving interventions. Early recognition may be challenging, particularly in the hospitalized patient, as clinical presentations can vary widely—and at times may be subtle—depending on the source of infection and host comorbidities. In sick patient populations, SIRS criteria have low diagnostic utility, as they are overly sensitive and nonspecific. In addition, in some particularly vulnerable populations such as the elderly or in those taking immunosuppressive medications, the clinical manifestation of both the infection and the SIRS response may be

markedly attenuated despite overwhelming infection. In these patients, the signs of organ dysfunction (e.g., delirium or oliguria) may be the only clinical clue of underlying severe sepsis. This underscores the importance of maintaining a high degree of clinical suspicion for the presence of sepsis as the underlying cause of any clinical deterioration in the critically ill patient. Given the adverse impact of recognition delays on the effectiveness of some interventions, it is prudent to initiate treatment presumptively for severe sepsis, unless—or until—an alternative diagnosis has been established.

Recognizing the inherent challenges in diagnosing sepsis, a 2001 consensus conference reviewed the conventional definitions of sepsis (see the definition section). Although the definitions were not altered, the consensus panel added other clinical signs, associated commonly with sepsis, to the existing list of criteria that should raise the suspicion of sepsis. These include unexplained hyperglycemia, change in mental status, significant edema, and a markedly positive fluid balance (> 20 mL/kg over 24 hours).

DIAGNOSIS

When suspecting a patient has sepsis, it is important to both establish the etiology of infection and assess the severity of sepsis. Finding a specific source of infection supports the diagnosis of sepsis (versus other systemic conditions), informs the appropriate choice of antibiotics, and facilitates source control. The severity of sepsis dictates which interventions, including ICU transfer, are indicated immediately.

In addition to a focused history and physical examination, it is important to obtain cultures and directed radiographic imaging to localize the source of infection. Ideally, obtain all cultures prior to antibiotic administration, to preserve their diagnostic sensitivity. However, pathogens grow in blood cultures in only half of even the most acutely ill patients.

Sepsis severity is readily established by physical exam and routine laboratory studies (see Table 10.1). Although some of these patients may be cared for on the general ward, when there is cardiovascular dysfunction, additional lifesaving interventions may be indicated. Specifically, septic shock or cryptic septic shock (lactate ≥ 4 mM/L, with a normal or high blood pressure) warrants early goal-directed therapy (EGDT) and prompt ICU transfer. Thus, a serum lactate should be obtained promptly in all patients with suspected sepsis, regardless of whether any other signs of organ dysfunction exist. In addition to high serum lactate levels (lactate ≥ 4 mM/L), intermediate lactate levels (i.e., ≥ 2 mmol/L) are associated with increased morbidity and mortality, independent of other organ dysfunction or level of blood pressure. The utility of serum lactate to risk-stratify the septic patient has been demonstrated across the continuum of care, from the prehospital environment to the emergency department to the ward and ICU patient. Conversely, the septic shock patient who maintains a normal serum lactate level throughout resuscitation appears to have a more favorable prognosis (Hernandez et al, 2012). Finally, in the proximal phase of resuscitation, transient hypotension (Marchick et al, 2009) and both abnormally low (< 70%) and abnormally high (≥ 90%) maximal $ScvO_2$ measures (Pope et al, 2011) identify patients at risk of subsequent adverse events (e.g., mortality).

ANTIMICROBIAL THERAPY

Timely administration of effective broad-spectrum antimicrobial therapy remains paramount in the initial management of the septic patient. Mortality increases nearly 8% for every hour delay in antibiotics administration beyond the first hour of hypotension. In addition, if the initial antimicrobial regimen is ineffective against the pathogen, mortality increases despite subsequent administration of appropriate antibiotics based on culture data. Therefore, empiric broad-spectrum antimicrobial therapy should be administered within 1 hour of identification of septic shock.

Furthermore, in patients with severe sepsis, a delay in administering antimicrobial therapy until after shock recognition is associated with increased mortality (Puskarich et al, 2011).

When choosing an empiric antibiotic regimen, always consider the likely source(s) of infection, coupled with prior culture results (i.e., patient colonization), courses of antimicrobials (to avoid the same class of agents), drug allergies, and the hospital antibiogram. Guidelines from the Infectious Disease Society of America and Surviving Sepsis Campaign have general recommendations for antimicrobial regimens suitable for specific sources of infection. These need to be modified by host- and hospital-specific factors. For example, immunosuppressed patients should be covered for all potential opportunistic pathogens.

After 3 days of treatment, de-escalate the antibiotic regimen to the narrowest spectrum possible based on available cultures, or discontinue antibiotics completely if an alternative diagnosis is established. However, if the patient fails to respond to the initial antibiotics, consider changing the drug regimen with a parallel, systematic search for a localized source of infection.

SOURCE CONTROL

Prompt removal or drainage of the likely source(s) of infection can be lifesaving, for similar reasons that antimicrobials must be given rapidly. The importance of physically removing a large quantity of pathogens from the body cannot be underscored. Antimicrobials alone will lyse or neutralize pathogens; however, these pathogens and their cellular debris may still cause harm through activation of a variety of immunologic reactions. Thus, it is imperative to search for and remove all likely sources of infection as soon as possible. If the patient remains in shock and no source is apparent, particularly if there are no localizing symptoms or signs, prompt removal of all endovascular lines and devices is indicated. In addition, once the patient has stabilized it is reasonable to perform cross-sectional imaging (computed tomography) of the chest, abdomen, and pelvis to search for a source.

FLUID AND PROTOCOL-DIRECTED RESUSCITATION

Fluid resuscitation is the mainstay of therapy in the initial management of the patient with septic (or cryptic septic) shock. Colloid is not superior to crystalloid, based on two meta-analyses and one large randomized controlled trial (RCT) (the SAFE study). In addition, a trial in septic shock patients compared Ringer's lactate to the colloid pentastarch, finding no difference in 28-day mortality and an increased incidence of acute renal failure and requirement for renal replacement therapy in subjects receiving pentastarch.

Administer a fluid challenge (500 to 1000 mL of crystalloid through a large-bore intravenous [IV] cannula over 5 to 15 minutes) in the patient with shock. Continue subsequent fluid boluses, provided circulatory parameters improve (e.g., heart rate, mean arterial pressure, extremity perfusion, urine output) without deleterious consequences (e.g., impaired oxygenation). In all patients with septic shock or cryptic septic shock, fluids and vasoactive agents should be guided by resuscitation end points including, but not limited to, what was used in the EGDT protocol (Rivers et al, 2001). This single center study demonstrated that an empirically designed resuscitation protocol, using central venous oxygen saturation as a resuscitation goal, reduced the incidence of shock and sepsis mortality. A controversial management question is whether protocol-directed resuscitation should be guided by lactate clearance or central venous oxygen saturation. While a randomized clinical trial found no evidence that one approach was superior to another, when viewed as complementary resuscitation end points that provide useful information independent of another, one need not select one or the other. Another controversial aspect of the EGDT protocol is the use of a packed red blood cell transfusion threshold more liberal than is currently recommended for ICU patients. However, a multicenter RCT is currently under way to further

evaluate the effectiveness of this protocol and the role of blood transfusions. Until these data are available, continued fluid boluses are recommended, rather than transfusing blood, to a goal central venous pressure of 8 to 12 mm Hg or greater, provided there is evidence for volume responsiveness and the additional fluid does not have deleterious effects (e.g., pulmonary edema or intra-abdominal hypertension).

After achieving the initial resuscitation goals and resolution of shock with a period of clinical stability, the goal becomes a net negative fluid balance. Oftentimes this occurs spontaneously, heralded by polyuria and negative fluid balance; however, diuretics may be required. Carefully monitor organ perfusion during diuretic-induced fluid mobilization to avoid secondary organ dysfunction.

VASOACTIVE THERAPY

The goals of resuscitation include maintaining an adequate mean arterial pressure and improving oxygen delivery (cardiac output) to support cerebral, coronary, and other systemic organ perfusion. Both goals are best achieved through IV crystalloid resuscitation; however, vasoactive medications may be required, both initially and even after adequate fluid resuscitation. Although the precise mean arterial pressure required to maintain adequate organ perfusion remains unknown, vasoactive agents are usually titrated to provide a mean arterial pressure (MAP) greater than 60 to 65 mm Hg. Studies show no improvement in organ perfusion targeting a higher MAP. Further, it is important to consider the individual patient's baseline blood pressure when setting target blood pressure. For example, organ perfusion may be compromised at a MAP of 60 to 65 in patients with chronic uncontrolled hypertension, and patients with chronic low blood pressure (e.g., liver failure, congestive heart failure) may tolerate a significantly lower MAP. Regardless, as therapies are titrated, always reassess the effectiveness (or adverse impact) of an intervention by following serial measurements of organ perfusion and function (e.g., physical exam, serum lactate measurements, central venous oxygenation, urine output, and mental status).

The best first-line vasopressor to use in patients with septic shock has been an area of controversy until recently. Based on the cardiovascular derangements in septic shock, an agent with both vasopressor and inotropic actions is preferred. As such, many published guidelines advocate the use of norepinephrine (NE) or dopamine as the first-line agent. Controlled clinical studies have not demonstrated a mortality benefit using any single agent. Specifically, there have been trials comparing NE to vasopressin (VP) and, separately, comparing norepinephrine (± dobutamine) to epinephrine, among others. A more recent multicenter, randomized controlled trial comparing dopamine to NE found that although there was no difference in mortality, dopamine use was associated with increased adverse events, most notably atrial fibrillation. Thus, the evidence now supports the use of NE as the preferred first-line agent. There are situations, however, when other agents may be preferable to use initially. For instance, it is recommended to infuse dopamine through a peripheral IV if a central venous catheter has not yet been placed. In addition, if hypotension is accompanied by cardiac arrhythmia, phenylephrine is preferred over norepinephrine to avoid exacerbating the arrhythmia due to the chronotropic properties of norepinephrine.

Regrettably, it is not uncommon for patients to remain hypotensive despite intravenous fluids and escalating doses of NE. In this situation, corticosteroids should be administered (see details below under anti-inflammatory therapies). In addition, when hypotension persists, increasing the dose of NE and/or adding other vasoactive agents may be required. VP is the preferred second-line agent, although there are no good outcome data to support this recommendation. The rationale for vasopressin, over other vasoactive agents, is that there is a well-described deficiency of vasopressin in septic shock. In addition, all other vasoactive medications stimulate the same alpha-receptor as norepinephrine (Table 10.2). Since none is a more potent

TABLE 10.2 ■ **Cardiovascular Pharmacology of Vasoactive Agents in Septic Shock**

Agent	Mechanism of Action	Typical Dose	Notes
Dobutamine	β_1, β_2 (3:1 ratio) >> α_1	2.5–20 mcg/kg/min	May worsen hypotension in the underresuscitated patient
Dopamine	D, β_1 > α_1, β_2	5–20 mcg/kg/min	Potential first-line agent
Epinephrine	α_1, β_1, β_2	1–10 mcg/min	Preferred second-line agent in pressor-refractory shock; β-adrenergic effects predominate at lower doses
Levosimendan	Calcium sensitizing agent and vasodilator	0.05–0.2 mcg/kg/min	Unclear role in septic shock
Norepinephrine	α_1 > β_{12}	1–30 mcg/min	Preferred first-line agent
Phenylephrine	α_1	40–200 mcg/min	Increased afterload via vasoconstriction, no direct inotropic effects
Vasopressin	V_1 receptors (vascular smooth muscle) V_2 receptors (renal collecting system)	0.01–0.04 U/min	Preferred second-line agent

α_1 denotes α_1 adrenergic receptor vasoconstriction; β_1 denotes β_1 adrenergic receptor activity; β_2 denotes β_2 adrenergic receptor vasodilation; D denotes dopamine receptors.

alpha agonist than NE, adding any of them at best would be similar to titrating up the dose of NE, and at worst would attenuate the vasopressor potency of NE, due to competitive inhibition of the alpha receptor by the weaker agonist—e.g., dopamine. Thus, when hypotension is refractory to low doses of NE, we recommend titrating up the dose, and when doses exceed 40-60 mcg/min initiate VP at 0.03 mcg/min. Of note, some would recommend the addition of VP to NE when the dose of NE is low (5-15 mcg/min). The rationale for this approach comes from a subset analysis derived from the Vasopressin Septic Shock Trial (VASST), which studied the effect of adding VP versus placebo to NE in patients with septic shock, and evidence that suggests that the presence of a B_2-adrenergic receptor genetic polymorphism may abrogate the adrenergic agonist response. Although VP had no mortality benefit overall in this study, there was a mortality benefit seen in patients with less severe shock, defined by the need for only low doses of NE (5-15 mcg/min). Finally, the optimal method of weaning vasopressors is unknown and requires further investigation.

ANTI-INFLAMMATORY THERAPY

The role of low-dose (or "stress-dose") corticosteroids in the treatment of severe sepsis and septic shock remains controversial. Annane and colleagues found a mortality benefit in a single-center randomized clinical trial when low-dose corticosteroids (hydrocortisone 50 mg IV q6h) and fludrocortisone (50 mcg enterally daily) were administered for 7 days to patients who did not respond to an adrenocorticotropic hormone stimulation test (≤9 mg/dL). In contrast, the Corticosteroid Therapy of Septic Shock (CORTICUS) study failed to confirm a mortality benefit, although the patients enrolled differed significantly (less ill) from those in the original Annane trial. Because both trials did demonstrate a significant reduction in the time to shock reversal in patients receiving low-dose corticosteroids, it is recommended that low-dose corticosteroids only be considered for patients with refractory septic shock.

TIGHT GLYCEMIC CONTROL

The therapeutic role of intensive insulin therapy, which has intuitive value given insulin's anti-inflammatory properties and the association between hyperglycemia and poor outcomes, has been called into question. Several studies of intensive insulin therapy failed to demonstrate a mortality benefit while simultaneously exposing an increased risk of hypoglycemia. Furthermore, inaccuracies inherent in point-of-care glucose monitoring may underestimate the incidence of hypoglycemia. It is prudent to control blood glucose in moderation, with a goal of 140 to 180 mg/dL to avoid marked hyperglycemia while reducing the risk of hypoglycemia.

ANTICOAGULATION THERAPY

The imbalance between pro- and anticoagulation in sepsis sequentially leads to a pro-coagulant state as well as the development of microthrombi and, ultimately, organ dysfunction. In controlled clinical trials, patients treated with recombinant tissue factor-pathway inhibitor and antithrombin III experienced more bleeding without mortality benefit. Similarly, initial studies of drotrecogin alfa (activated protein C, 24 mcg/kg/hour for 96 hours) in the sickest subgroup of patients (with Acute Physiology and Chronic Health Evaluation Scores ≥25) yielded a 13% absolute risk reduction in mortality. However, subsequent studies failed to confirm this clinical benefit and revealed the known hemorrhagic complications of this therapy, leading to withdrawal from the market.

NUTRITIONAL SUPPORT

In a single-center, small, randomized controlled trial, Pontes-Arruda and colleagues employed an anti-inflammatory enteral feeding strategy that decreased morbidity and mortality. Based on these findings, an early, appropriate enteral feeding with eicosapentaenoic acid, gamma-linoleic acid, and antioxidants was considered of potential benefit as an adjunctive treatment strategy in patients with severe sepsis. However, after a recent trial of this strategy in patients with acute lung injury failed to demonstrate a benefit, and suggested harm, the optimal approach to nutritional support in the critically ill patient remains elusive.

REFRACTORY SHOCK

When patients fail to respond to antibiotics, fluid resuscitation, vasoactive medications, and corticosteroids, there are several considerations to think about. Most importantly, one should review the antimicrobial regimen and consider broadening for uncovered pathogens. In addition, one should do an exhaustive search for an undrained focus of infection and also consider alternative diagnoses for distributive shock. It is also possible that shock is persisting due to a side effect of a newly prescribed medication—e.g., anaphylaxis due to an antimicrobial. A less well-known medication side effect is dynamic left ventricular outflow tract (LVOT) obstruction due to inotropes. This phenomenon can occur in septic patients who are under-resuscitated (small ventricular size) and should be considered when a systolic ejection murmur is heard in the setting of persistent shock, particularly in woman (smaller ventricle) with a history of hypertension. The LVOT obstruction and systolic murmer are related and are both caused by systolic anterior motion of the anterior leaflet of the mitral valve. This occurs because of the Venturi effect on the valve leaflet caused by the rapid velocity of blood flow through the narrowed aortic outflow tract. This diagnosis can be confirmed easily with an echocardiogram that reveals an underfilled, hyperdynamic left ventricle and an LVOT gradient on Doppler ultrasound (Chockalingam et al, 2009). These cases should be managed with aggressive fluid resuscitation, de-escalation of the inotropic agent, and if necessary

the addition of a beta-blocker. Another consideration for persistent shock is rebound hypotension in the patient recently receiving corticosteroids.

Additional suggestions for management include re-considering the goal mean arterial pressure, given evidence that increased vasopressor load is associated with adverse events (e.g., arrhythmia, ischemia) and mortality, and in the case of febrile refractory septic shock, temperature targeted management to normothermia given that this approach may lead to faster resolution of shock and improved short-term survival.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 11

Vascular Access Issues and Procedures

Christopher T. Dibble ■ Benjamin A. Kohl ■ Paul N. Lanken

Obtaining access to the vasculature is an essential skill for clinicians in intensive care units (ICUs). Arterial catheterization is used to continuously monitor blood pressure and to obtain blood for arterial blood gas analysis and other laboratory tests. Central venous catheterization permits measurement of central venous pressures (CVPs); rapid infusion of fluids; and central administration of certain agents, such as calcium, potassium, vasoactive agents, or hyperalimentation solutions. This chapter begins with a brief overview of the use of ultrasound to guide vascular access, followed by a description of the indications, techniques, and risks of cannulation of arteries, veins, and pulmonary artery.

Bedside Ultrasonography in the ICU

Introduction

The dramatic improvements in ultrasound technology have allowed for a growing role for its use in both diagnostic and therapeutic procedures in the ICU. Compared to the traditional landmark-guided approach, when used by experienced individuals to guide vascular cannulation, ultrasound has been shown to reduce the number of attempts, incidence of complications, and time to successful catheterization.. This section focuses on the use of two-dimensional ultrasound and Doppler techniques in the ICU.

TECHNICAL CONSIDERATIONS

Before beginning any procedure with ultrasound guidance, the operator must have familiarity with the equipment. This includes, but is not limited to, knowledge of the various types of probes, the specific ultrasound machine in use, and appropriate knowledge of the anatomy to be interrogated. Additionally, an understanding of ultrasound physics and image interpretation (as well as knowledge of ultrasound artifacts) is necessary. Vascular access typically employs a linear array transducer. This probe can be recognized by the flat front on the transducer. It will produce a square image on the screen, in contrast to the wedge-shaped image of a phased-array probe. On one side of the probe is an indicator that corresponds to the marker on the left-hand side of the display screen.

The depth of the display and image gain should be set so that the structure of interest is in the middle of the screen and tissue density is appropriately shaded, respectively.

METHODOLOGY

Ultrasound can be used in both static and dynamic capacities to aid in vascular access. Static ultrasound is the use of imaging to localize, characterize, and mark the vessel prior to beginning

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the procedure. In contrast, dynamic ultrasound uses imaging to visualize the needle and the vessel in real time during the procedure and to guide puncture of the vessel. It is optimal to apply both techniques: (1) assess vessel location and patency prior to preparing the patient and (2) perform the procedure using dynamic ultrasound guidance.

Vessels can be imaged in a transverse or longitudinal fashion. Transverse imaging allows for easy identification of surrounding structures (e.g., carotid artery during internal jugular cannulation). This technique, however, requires greater skill than longitudinal imaging as it is often difficult to differentiate between the tip and shaft of the needle. Without knowing where the tip of the needle is at all times, ultrasound becomes useless and can be dangerous as it may give a false sense of security. Longitudinal imaging allows one to visualize the needle throughout its length and as it pierces the vessel. This, however, requires greater coordination as the operator must ensure that the ultrasound plane of imaging does not move during needle insertion.

After adequate images are obtained, the skin is entered with the needle above the vessel. It often takes one hand to hold the skin taught and the other to pierce the skin with the needle. Next, using the dominant hand to guide the needle and the nondominant hand to hold the probe, the needle can be visualized and advanced. A needle guide to align the probe with needle can be helpful for beginners but is not necessary. The needle appears as a hyperechoic (white) structure. If transverse imaging is utilized, it is helpful to gently fan or rock the probe to bring the tip of the needle into and out of the plane of the image. This allows one to determine if he or she is seeing the shaft or the tip of the needle on the screen.

Arterial Catheterization

INDICATIONS

Measuring blood pressure with an intra-arterial catheter is preferable to non-invasive methods when there is a need for frequent blood pressure readings. Each of the determinants of blood pressure (blood volume, systemic vascular resistance, and cardiac contractility) can change rapidly under certain circumstances. For example, effective blood volume changes minute by minute in response to major gastrointestinal bleeding or to large increases in intrathoracic pressure. Systemic vascular resistance can also vary rapidly with changes in patient temperature (e.g., rewarming after therapeutic hypothermia) or in response to administration of vasoactive drugs. Drugs that depress cardiac contractility or rate can also cause rapid decreases in blood pressure. Newer forms of hemodynamic monitoring that employ analysis of the arterial waveform or variations in arterial pulse pressure to determine cardiac output or predict fluid responsiveness also require arterial catheterization. In addition, arterial access may be required to sample arterial blood to determine pH, Pa_{O_2}, and Pa_{CO_2} frequently in patients with acute respiratory failure or acid-base disorders. Finally, the need for frequent phlebotomy may warrant insertion of an arterial catheter for patient comfort.

SITES

A number of superficial arteries are used for arterial catheterization in the adult, including the radial, ulnar, brachial, axillary, femoral, dorsalis pedis, and posterior tibial arteries (Table 11.1). Although the radial artery is the most commonly used site, alternative sites may be useful in certain situations. For example, when the radial artery is not palpable, the femoral artery is an acceptable alternative. Although some ICU clinicians perform an Allen test before radial artery cannulation to document the presence of collateral circulation (via the ulnar artery), many others do not. The medical literature, including large series of patients receiving radial artery cannulation, is equivocal regarding any benefit to including this test prior to cannulation. In addition,

As with all procedures on ICU patients, the operator should observe standard safety measures prior to starting the procedures, including a "time out" or "pause" for safety, and document the pause (see Chapter 109). At a minimum, this should confirm that the following are correct: (1) the patient, (2) the procedure, and (3) the extremity and laterality (right versus left side). To perform vascular access using dynamic ultrasound, the ultrasound should be positioned in a manner that allows the practitioner easy viewing access without strain or discomfort. After the site is prepped in a standard and sterile manner, the operator dons hat, gown, and gloves. The sterile area should be draped, and ultrasound gel is placed inside a sterile plastic sleeve. An assistant then lowers the ultrasound probe into the sleeve taking care to avoid contamination of the operator, the sterile field, or the outer surface of the sleeve. The sleeve should be extended so that it covers both probe and cable, allowing the operator mobility without concern for impairing the sterility of the field. Sterile gel is then placed on the patient over the site of interest.

The probe can now be used to define the internal anatomy. Most fluid, including blood, appears black and hypoechoic. Veins are readily identified, as they are typically larger and more compressible than arteries. Additionally, if color flow Doppler is utilized, pulsatile flow is usually not seen in veins. Note that reliance solely on this latter feature may cause confusion in patients with severe tricuspid insufficiency. Additionally, in patients who are severely hypotensive, arteries may exhibit easy compressibility, making it more difficult to differentiate them from veins.

TABLE 11.1 ■ **Sites for Arterial Catheterization**

Artery	Advantages	Disadvantages	Comments
Radial	Accessible, collaterals present, patient comfort, lower risk with coagulopathy	Site of prior sticks, can be difficult in patients with shock	
Ulnar	Accessible, collaterals present	Small caliber in most patients	May result in ulnar nerve injury
Brachial	Superficial	No collaterals, more difficult than radial to cannulate, may result in median nerve injury	
Axillary	Collaterals present	Difficult to cannulate, deep location	Use ≥ 3-inch long catheter
Femoral	Good waveform fidelity, easy to cannulate, preferred site for obtaining emergency access	Patient may not sit or bend legs, retroperitoneal bleeding if puncture above the inguinal ligament	Use ≥ 6-inch long catheter
Dorsalis pedis	Superficial, collaterals usually present	Lower extremity must be immobilized, can be difficult to cannulate	
Posterior tibial	Superficial, collaterals usually present	Small caliber in most patients	

there is no consensus on the definition or significance of an abnormal test. Clearly, after arterial catheterization of any site, the distal extremity must be monitored for signs and symptoms of ischemia. If there is concern for ischemia, the arterial catheter should be removed and a vascular surgeon should be consulted for immediate evaluation.

Common upper extremity alternatives to the radial artery include the brachial and axillary arteries. The brachial artery is superficial, readily palpated, and easily imaged by ultrasound; however, it has the disadvantage of being an anatomic end-artery that lacks a collateral circulation. Consequently, some intensivists prefer the axillary artery because it has a collateral circulation; however, the axillary artery can be more difficult to cannulate as well as to repair surgically in case of dissection or thrombosis.

In the lower extremity, the femoral artery is the preferred site for arterial cannulation. It is easy to access, and its arterial waveform usually demonstrates good fidelity. Patients with indwelling femoral catheters should not be mobilized from bed to chair to prevent injury to the artery. In addition, there are serious complications that can result from the procedure itself, including retroperitoneal bleeding (when the artery is punctured above the inguinal ligament) and atheromatous emboli in patients with diffuse atherosclerosis. The dorsalis pedis artery is an alternative in the lower extremity because it generally has good collateral flow.

INSERTION METHODS

There are two common approaches to cannulating an artery in the ICU: direct cannulation of the vessel and the modified Seldinger technique. The direct approach involves insertion of the needle into the vessel lumen until arterial blood is identified. At this point the catheter is gently

threaded over the needle into the artery. The direct approach can be used for catheterization of smaller vessels; however, it is often more difficult to perform and is not suggested for inexperienced operators.

The modified Seldinger technique is a multistage procedure (Figure 11.1). The first step involves insertion of the needle into the vessel lumen. Ultrasound guidance may be helpful during this step. The second step involves passing a thin guide wire through the needle into the lumen. After the wire is in the vessel lumen, the introducer needle is removed while the operator maintains control of the guide wire. Next, a plastic catheter is threaded over the wire into the vessel. The wire is now removed from the catheter lumen. Success is confirmed by the return of pulsatile blood from the catheter. Care should be taken to avoid traumatizing the vessel. The wire typically has a flexible, often J-shaped, tip and only this end of the wire should enter the vessel. The wire should never be advanced if resistance is met. Finally, a complication of this technique is inadvertent loss of the wire into the vessel, which can be avoided by maintaining control of some portion of the wire throughout the procedure.

The traditional modified Seldinger technique is used for larger vessels such as the femoral artery; however, two variations are helpful, particularly for smaller vessels such as the radial artery. The first is use of arterial line kits that have an integrated needle, catheter, and guide wire. The kits are used in a similar fashion as described previously, except once the vessel is entered with needle, the wire is advanced, and the catheter is simply advanced over the needle and into the vessel.

The second method utilizes a separate guide wire. After puncturing the skin with the catheter and visualizing arterial blood in the reservoir, the catheter and needle are advanced slightly further so that the back wall of the artery is punctured (the so-called through-and-through technique). The needle is then removed. The catheter is very slowly withdrawn into the vessel. When pulsatile blood flow is again obtained, a small guide wire is advanced through the catheter into the vessel lumen. Finally, the catheter is advanced over the wire into the vessel.

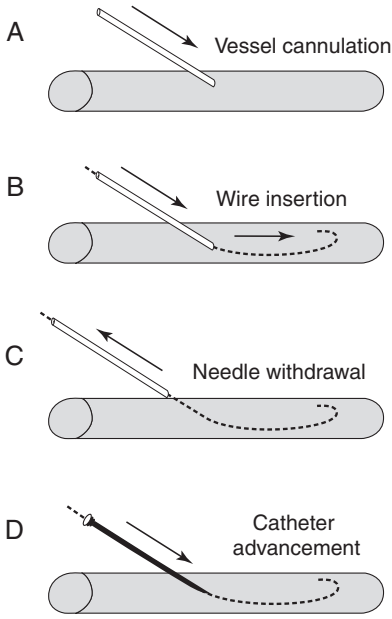


Figure 11.1 The modified Seldinger technique. **A,** Needle is inserted into the lumen of the selected vessel. **B,** Thin guide wire *(dashed line),* with flexible end first, is inserted through the needle into the vessel. **C,** Needle is removed over the wire while operator maintains control of the wire. **D,** Plastic catheter is inserted over the wire into the lumen.

COMPLICATIONS

Risks of arterial catheterization include infection, thrombosis, and hemorrhage. The risk of arterial catheter-related bloodstream infection is controversial, but it is certainly lower than the risk of central venous catheter infection. There are minimal data to support the practice of routine changes in cannula and/or cannulation site and such a practice is discouraged. While bloodstream infection from arterial catheters is uncommon, colonization of the hubs of their three-way stopcocks by bacteria, such as coagulase-negative staphylococcal species, is common. Consequently, one should never use an arterial catheter to obtain blood cultures except at the time of its first insertion.

Thrombosis of arterial lines is most likely to occur when the cannulated vessel is anatomically abnormal (calcified, narrowed) or if there is circulatory shock and impaired blood flow. Central (retrograde) embolization of air bubbles or thrombi with serious consequences can occur if an arterial catheter is flushed vigorously.

Peripheral Venous Catheterization

Peripheral intravenous (IV) catheters are present in all patients in the ICU. Insertion is typically performed using a catheter-over-needle technique. Ultrasound has been shown to be helpful when venous cannulation is particularly difficult. The primary advantages of peripheral IV catheters include the ease of insertion, the low rate of serious infection, and the ability to infuse a large volume of fluid quickly. Indeed, because of the lower resistance of a shorter catheter, two large well-placed, peripheral IVs are superior to many forms of central venous access for large volume resuscitation. This is particularly relevant in conditions such as active gastrointestinal (GI) bleeding where large volumes may need to be rapidly infused.

The use of peripheral IVs in the ICU is limited by many factors. It is often difficult to locate suitable veins in critically ill, obese, or edematous patients. Moreover, standard peripheral IVs should be replaced every 72 to 96 hours to reduce the risk of phlebitis. Finally, most hypertonic, irritant, and vasoactive substances cannot be safely infused into a peripheral vein.

A midline catheter can overcome some of the limitations of a peripheral IV. The risk of phlebitis is lower than that of a peripheral IV; therefore, midline catheters do not need to be routinely replaced. Midline catheters are typically 3 to 8 inches long and inserted into a large vein in the antecubital fossa under ultrasound guidance. Like peripheral IV catheters, midline catheters do not enter the central veins and thus are not suitable for hypertonic, irritant, or vasoactive substances.

In cases of ongoing or anticipated exsanguination, peripheral cannulation of a large vein may be necessary to allow rapid infusion of fluids. Large catheters (7 or 8 Fr) exist for this purpose and are typically inserted into an extremity (often the antecubital fossa) via a standard Seldinger technique. Ultrasonography can be very helpful for determining the location of an appropriately sized vessel in addition to confirming placement. Several commercially available kits include everything necessary (e.g., scalpel, wire, catheter) to appropriately cannulate such a vessel in an urgent setting.

Central Venous Catheterization

INDICATIONS

Central veins are cannulated for a variety of reasons in the ICU, including monitoring of pressure and central venous oxygen saturation as well as administration of fluids. Patients who lack suitable veins for reliable peripheral venous access often require central venous catheters. Central

Two uncommon complications of arterial cannulation are the formation of an arteriovenous fistula or the development of a pseudoaneurysm after removal of the catheter. These occur more frequently when larger arteries are cannulated. Finally, hemorrhage can occur at the time of insertion if the vessel is traumatized, or after removal of the catheter, especially in patients who have a coagulopathy or who are undergoing thrombolysis. Hemorrhage from a catheterization site should be treated with manual application of firm direct pressure over the site of vessel puncture site until hemostasis is achieved. Uncontrolled hemorrhage from a radial artery may result in a compartment syndrome of the forearm.

venous access is also indicated for the administration of vasoactive agents, hypertonic fluids, and other substances that may be injurious to peripheral veins (e.g., calcium chloride and vasopressors). Vasopressors can cause constriction and vessel injury when administered into small peripheral veins. Administering them centrally decreases the time between changes in dose and onset of effect because of the shorter "path length" between the drug infusion site and site of action. Finally, central venous access is required for pulmonary artery catheterization, temporary cardiac pacing, plasmapheresis, and hemodialysis.

SITES

The external and internal jugular, subclavian, and femoral veins are the most frequently used sites for central venous cannulation in the ICU (Table 11.2). In addition, the central circulation can also be accessed using peripherally inserted central (PIC) catheters that are threaded from the basilic or axillary veins into the superior vena cava.

The external jugular vein is both superficial and visible in most thin patients but is difficult to use for central access. Prominent venous valves and tortuosity of the peripheral vessel frequently make threading a catheter into the central circulation difficult. The internal jugular vein is technically more difficult to access than the external when using a traditional landmark-based approach because it lies deeper in the neck and is adjacent to the carotid artery, which can be inadvertently

TABLE 11.2 ■ **Sites for Central Venous Cannulation**

Vein	Advantages	Disadvantages	Comments
External jugular	Superficial, visible, easy to tamponade bleeding	Difficult to pass catheter into central veins	Often has two valves and a tortuous course to thorax
Internal jugular	Reliable central access, no venous valves; location of vein and carotid artery can be easily identified by bedside ultrasound evaluation	Close to carotid artery, difficult to keep site dressed well, higher risk of catheter-associated infection than subclavian vein	Use right internal jugular preferably to insert pulmonary artery catheter (more direct route); right internal jugular also avoids risk of trauma to thoracic duct
Subclavian	Reliable central access	Up to 5% risk of complications (pneumothorax and bleeding)	Reposition using fluoroscopy if tip is in internal jugular vein before infusing pressors or hypertonic solutions
Femoral	Easy central access	High risk for nosocomial infection; requires immobilization of patient	Access of choice for emergencies
Basilic	Easy access for PIC catheter*	Catheter may become occluded if elbow is bent	Confirm proper location of tip in superior vena cava by fluoroscopy or chest radiography
Axillary	Reliable vein to use for PIC catheter	Needs ultrasound to localize; more difficult to cannulate	Requires a standard PIC catheter to be cut to proper length

*PIC catheter, peripherally inserted central catheter.

punctured during catheterization attempts. Fortunately, the internal jugular vein is easily imaged with ultrasound. Once the internal jugular vein is entered, the internal jugular catheter is readily advanced because the vessel is typically straight and lacks valves. Both the external and internal jugular veins are more difficult to cannulate in obese patients and in patients with short necks. The subclavian vein is an alternative site with a relatively constant anatomic location but with a higher incidence of pneumothorax during insertion than the internal jugular vein. The subclavian site should be avoided if possible in patients who would not tolerate a pneumothorax. It is easier to maintain sterile dressings over the subclavian site, and the risk of infection is lower than it is for the jugular or femoral sites. The subclavian site is therefore preferred for long-term venous access or in patients with a tracheostomy. Because the subclavian vein is not easily compressible, it should be avoided if possible in coagulopathic patients.

The femoral vein is the least preferred site because of a higher risk of infectious complications and loss of patient mobility. Use of this site is also undesirable if one wants access for passage of a pulmonary artery catheter or a transvenous pacing wire because fluoroscopy is typically required to guide the catheter or wire from the inferior vena cava into the right ventricle. The right internal jugular and the left subclavian veins provide the most anatomically direct routes to the heart when one is inserting such devices. The right internal jugular vein is the preferred venous access for inserting hemodialysis or apheresis catheters.

PIC catheters are particularly useful for long-term venous access and in the chronic phase of critical illness and do not impede patient mobility. However, PIC catheters have several important limitations when used in the ICU. The infection rate associated with PIC catheters is probably similar to that of traditional central venous catheters. In addition, their long, narrow lumens have high resistance and do not allow for the high flow rates required for volume resuscitation. Most institutions use only single or double lumen PIC catheters that are often inadequate for critical care patients who require multiple infusions. Finally, PIC catheters may be associated with a higher incidence of upper extremity deep vein thrombosis when compared to traditional central venous access.

INSERTION METHODS

Like arterial catheters, the central venous vessels are most commonly cannulated using the modified Seldinger technique. Most intensivists access the internal jugular vein, using the middle approach (Figure 11.2), or the subclavian vein, using the infraclavicular approach (Figure 11.3). Other approaches to the internal jugular vein (anterior or posterior approach) are available but are used less commonly. For internal jugular cannulations, one can decrease the risk of complications by using ultrasonographic guidance. Ultrasonography can be used to image the selected vessel's course and depth before the procedure. When possible, ultrasonography should be used in a real-time fashion to guide vessel puncture as described earlier. In contrast, the subclavian vein is more difficult to visualize by ultrasound and is usually cannulated using anatomic landmarks.

All central vessels should be cannulated in a sterile manner, and care should be taken to prevent air embolism, hemorrhage, and nerve injury. Evidence-based practices to reduce infectious complications include preparing the site by scrubbing widely with a chlorhexidine-based solution; use of sterile gown, gloves, mask, and cap by the operator; and widely draping the patient to prevent inadvertent catheter contamination (Chapter 14). After preparation, local anesthetic is liberally infiltrated into the area around the vessel (if the patient is awake), which is then cannulated using the modified Seldinger technique (see Figure 11.1). The electrocardiogram is monitored for arrhythmias during guide wire and catheter insertion. Vessel cannulation is facilitated by positioning the desired vessel below the level of the heart; Trendelenburg's position is used for the neck and thoracic vessels, and reverse Trendelenburg's position is used for the femoral vein. These positions distend the target vessel and, importantly, help to prevent entrainment of air into the vessel.

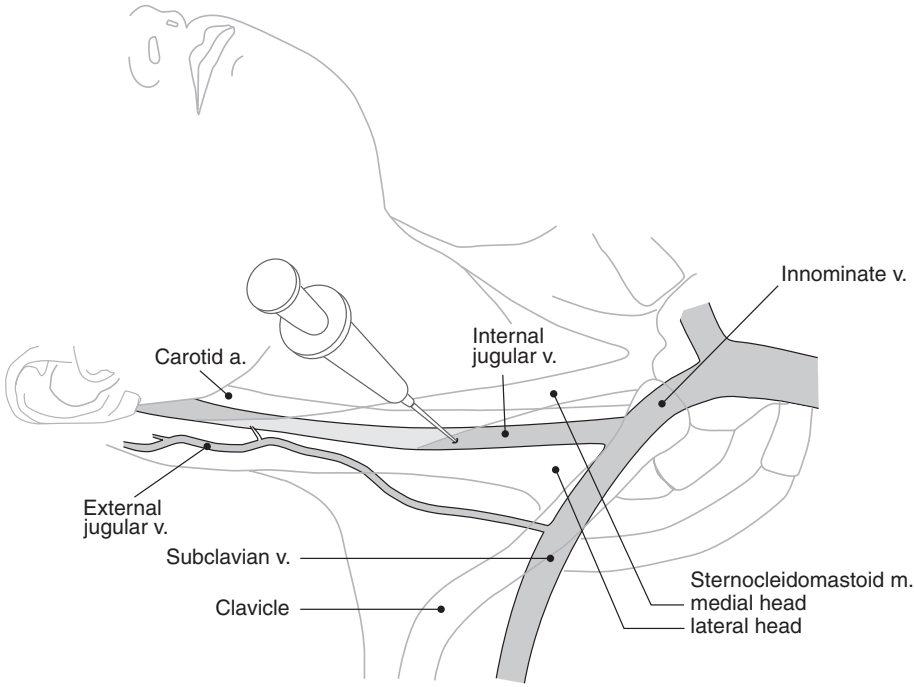


Figure 11.2 The middle approach for cannulation of the right internal jugular vein. The needle is inserted at the apex of the triangle formed by the medial (sternal) and lateral (clavicular) heads of the sternocleidomastoid muscle and the clavicle. The needle, inserted at a 45-degree angle in the direction of the ipsilateral nipple, usually enters the vein after 2 to 4 cm of insertion. *(Redrawn from Preas HL, Suffredini AF: Pulmonary artery catheterization: insertion and quality control. In Tobin MJ [ed]: Principles and Practice of Intensive Care Monitoring. New York: McGraw-Hill, 1998, pp 773-795.)*

COMPLICATIONS

Although central venous cannulation is generally a safe procedure, serious complications can occur if appropriate care is not taken (Table 11.3). Careful preparation, use of ultrasound, utilizing standard infection control and safety precautions, and reversal of existing coagulopathies can prevent most of these complications.

Infusion of certain agents (e.g., vasopressors) into the arterial circulation can be catastrophic; therefore, venous placement should be confirmed before the catheter is used. Before the vessel is dilated and the catheter is inserted into the vessel, ultrasound can be used to confirm the venous location of the guide wire. Additionally, venous pressure in the target vessel can be transduced by using a 20- to 30-cm piece of sterile IV extension tubing (included in some central line kits) as a manometer. To transduce pressure, the extension tubing is attached to an angiocatheter, held upright, and a column of blood is drawn up using a syringe attached to the other end of the tubing. The syringe is then removed. If the location of the catheter is arterial, the column will pulsate; if the location is venous, the column will fall. Once venous pressure is confirmed, the guide wire is reinserted through the angiocatheter and the vessel cannulation is completed. Great care should be taken not to allow air to enter the vasculature during this procedure. Alternatively, venous pressure can be transduced directly from the introducer needle, without inserting an angiocatheter; however, this process may be less safe and reliable than using the angiocatheter technique as it can be difficult to maintain the position of the needle tip within the vessel lumen. The angiocatheter

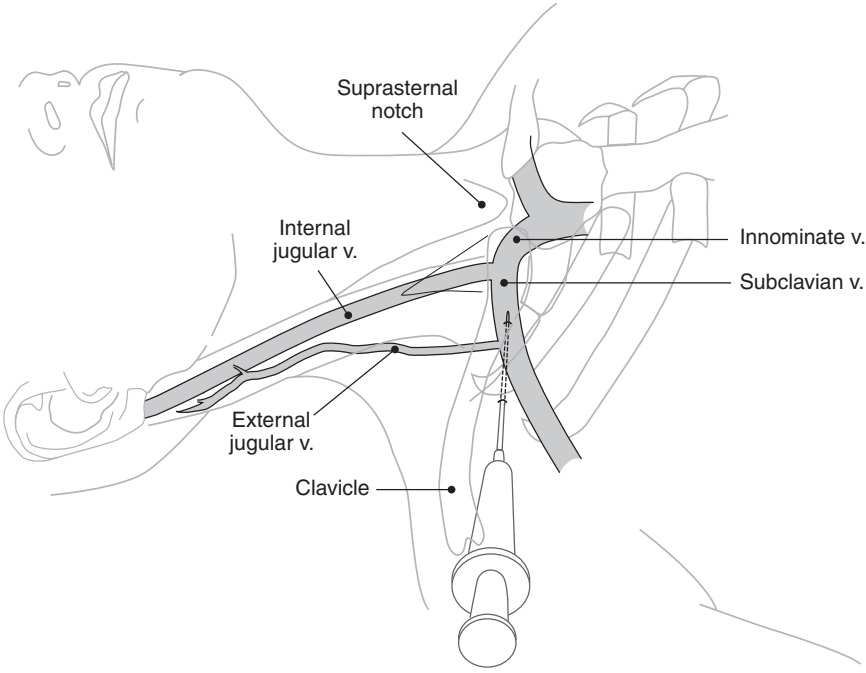


Figure 11.3 The infraclavicular approach for cannulation of the right subclavian vein. The patient should be supine with head down 30 degrees (some intensivists insert a rolled-up towel between the patient's scapulas, allowing the medial part of the clavicle to rise). The needle is inserted 1 cm below the most raised portion of the clavicle. This insertion point may be located slightly beyond the halfway point (between the medial and lateral clavicular ends), or at the junction between the middle and distal thirds of the clavicle, or in between. The needle is directed toward the suprasternal notch (which is palpated by the operator's other hand), keeping the needle parallel to the frontal plane and the undersurface of the clavicle. The bevel of the needle should be directed caudally to facilitate placement of the wire into the innominate rather than the internal jugular vein. The needle is advanced while keeping the syringe under modest suction, and it should enter the vessel after 3 to 5 cm of insertion. If there is no blood return, the needle should be slowly withdrawn while continuing to keep the syringe under suction. *(Redrawn from Preas HL, Suffredini AF: Pulmonary artery catheterization: insertion and quality control. In Tobin MJ [ed]: Principles and Practice of Intensive Care Monitoring. New York: McGraw-Hill, 1998, pp 773-795.)*

technique should not be used for vessels that are very deep, as the catheter may not be long enough to remain securely in the vessel after the wire is removed.

If identification of the vessel remains unclear, a sample of blood can be sent for Po_2 analysis to distinguish between vein and artery. Simultaneous measurement of an arterial blood gas from an arterial catheter is often helpful. In addition, the proper position of the tip is confirmed by routinely obtaining a postprocedure chest radiograph before use in most non-emergency ICU situations. The routine post-insertion chest radiograph can also identify procedure-related pneumothoraces that occur immediately, although some of these may be delayed.

A number of factors can reduce the risk of catheter-related infections and are described previously as well as in Chapter 14. In addition, antimicrobial-impregnated catheters are less susceptible to catheter-associated infections and should be considered for high-risk patients when the catheter may be in place for more than 5 days.

As a rule, the catheter site should be changed when there are signs of local infection. Likewise, when sepsis or septic shock is present, in the absence of another source of infection, removal of the catheter should be strongly considered. Some institutions culture the tip of the catheter when

TABLE 11.3 ■ **Complications of Vascular Catheterization**

Type of Catheter	Complication
Central venous catheter	Arrhythmias (if tip or guide wire enters right ventricle)
	Arterial puncture and hemorrhage
	Catheter-associated infection (femoral risk > internal jugular risk > subclavian risk)
	Hemothorax (especially with subclavian)
	Inadvertent arterial cannulation
	Pneumothorax (subclavian risk > internal jugular risk)
	Thoracic duct injury (with left internal jugular site)
	Thrombosis
	Venous air embolism
Arterial catheter	Arteriovenous fistula (after removal)
	Distal ischemia or emboli
	Hemorrhage (during insertion attempt and after removal)
	Heparin-induced thrombocytopenia (if heparin is used)
	Nerve injury
	Pseudoaneurysm (after removal)
Pulmonary artery catheter*	Right bundle branch block (see Chapter 34)
	Pulmonary artery rupture and hemorrhage
	Ventricular arrhythmias during passage through right ventricle

*Insertion of introducer and sheath has the same complications as listed under venous catheter.

catheter-related bloodstream infection is suspected. This practice is controversial as the sensitivity and specificity of this technique are limited and reliable results are only obtained when meticulous technique is used. Some studies suggest that the risk of catheter-associated infection and bacteremia, especially from pulmonary artery catheters, increases roughly 4 days after placement; however, routine catheter changes to prevent infection are ineffective and not recommended. Routine site changes do not decrease the rate of infections but do increase the rate of serious mechanical complications, such as pneumothorax. Routine "over the wire" changes are also not recommended.

Pulmonary Artery Catheterization

INDICATIONS

Pulmonary artery (PA) catheters are used in the ICU to aid in the assessment of hemodynamic status. Whereas PA catheters were previously used routinely in the management of heart failure, circulatory shock, and acute cardiac and noncardiac pulmonary edema, later clinical studies failed to support their efficacy for any specific condition in the ICU. Although it is now clear that pulmonary artery catheters should not routinely be placed for hemodynamic monitoring in the ICU, many experts find pulmonary artery catheters of value in certain clinical circumstances (e.g., suspected cardiac tamponade and heart failure unresponsive to appropriate therapy).

SITES

Pulmonary artery catheters require insertion of a large bore venous cannula ("sheath") that, in general, should be 0.5 to 1 Fr larger than the PA catheter to be used. If placement is in either the

right internal jugular vein or the left subclavian vein, the catheter can typically be "flow directed" (via balloon inflation) into the pulmonary artery. Other sites of insertion may require fluoroscopy to aid with proper positioning.

INSERTION

The PA catheter is prepared prior to insertion by attaching sterile stopcocks on the distal (PA port), right atrial, and right ventricular ports (if applicable). Intraluminal air is removed by flushing all ports with sterile saline. The three-way connector that is connected to the PA's distal port is then attached to a calibrated and zeroed-pressure transducer. Before insertion, one should test the integrity of the balloon. The balloon should inflate symmetrically and, when fully inflated, protrude beyond the tip of the catheter to avoid damage to the right ventricular (RV) wall as it floats through the RV (even with this precaution, a PA catheter may cause a right bundle branch block during its passage through the RV). If the PA catheter is to be left in place, the catheter can be threaded through a sterile sleeve that maintains catheter sterility and allows for small adjustments in positioning after the sterile field is removed.

The PA catheter with the balloon deflated is inserted through the diaphragm of the introducer sheath and advanced toward the right atrium. This should be done while monitoring surface electrocardiographic tracings and pressure waveform tracings obtained from the distal tip of the catheter. After advancing to the vicinity of the right atrium (usually 10 to 15 cm for subclavian vein access and 15 to 20 cm for internal jugular vein access), one should confirm that the pressure tracings show the appropriate respiratory variations. If present, the balloon is inflated fully but slowly with 1.5 mL of air (stopping inflation if any resistance is met) and advanced steadily through the RV and into the pulmonary artery to a wedged position. Pressure tracings should be recorded during this passage to confirm proper serial locations of the tip during its passage and to obtain measurements of right atrial (RA), RV, PA, and PA wedge pressure (PAWP) (Figure 11.4). After obtaining a wedge pressure, the balloon should be deflated and the catheter, if it is to remain in place, should be withdrawn 3 to 5 cm to a more proximal position within the PA. Because the tips of PA catheters may migrate distally and may become wedged spontaneously in such a position, monitoring for such a possibility is mandatory. This includes continuous pressure tracings and ECG monitoring as well as consideration for daily chest radiographs (Chapter 13).

HEMODYNAMIC MEASUREMENTS

Accurate measurements of the PAWP depend on the ability to recognize the pressure tracings of the wedged catheter while taking into account fluctuations in pleural pressure that result from respiratory variations. The PAWP is measured as an end-expiratory value and not as a mean value over the entire respiratory cycle. This point is chosen to minimize the impact of intrapleural pressure on PAWP.

Measurement of the PAWP in patients who are being mechanically ventilated requires an understanding of cardiopulmonary physiology. In order to identify end expiration, clinicians are often taught to select the lowest point on the PAWP waveform for a mechanically ventilated patient (Figure 11.5). This can lead to errors in measurement of the PAWP, as some patients actively inhale on the ventilator. In such patients the apparent PAWP will decline during inhalation and thus may not represent a clinically valid number. To avoid making such errors, a simultaneous airway pressure tracing can be recorded on the same dual channel hard copy recording strip as the PAWP and can more reliably signal end-expiration. End-expiration measurements have been standardized in some research protocols to be taken as a mean value between 400 msec to 200 msec (one large box [= 5 small boxes] on the ECG paper before the start of inspiration. The latter is evidenced by the start of a negative deflection (in a patient-triggered breath) or of

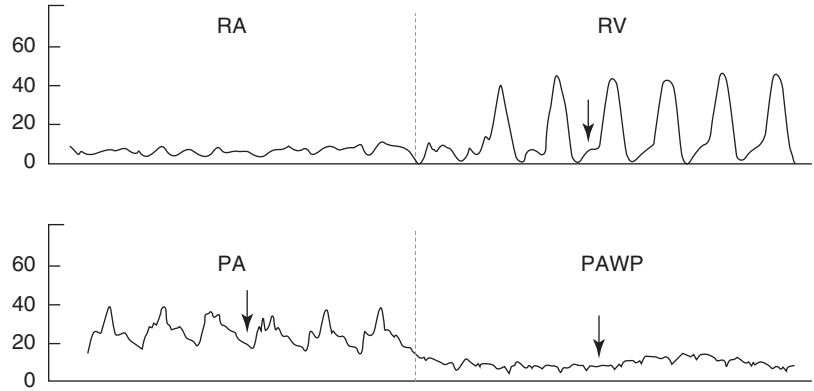


Figure 11.4 Pulmonary artery catheter pressure waveforms in a patient with acute respiratory distress syndrome (ARDS) receiving mechanical ventilation: right atrium (RA), right ventricle (RV), pulmonary artery (PA), and pulmonary artery wedge pressure (PAWP). One can distinguish RV from PA waveforms because RV pressure rises in diastole *(arrow)* whereas PA diastolic pressure falls *(arrow)*.

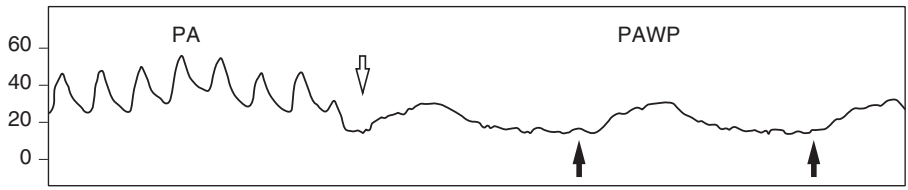


Figure 11.5 Pulmonary artery catheter waveforms from a patient receiving mechanical ventilation. The tip of the catheter resides in the pulmonary artery (PA) with the balloon deflated. The balloon is then inflated *(open arrow),* resulting in pulmonary artery wedge pressure (PAWP) tracing. Measurement of PAWP should be made at end expiration *(closed arrows)*. The positive deflections following end-expiration reflect positive-pressure inspirations.

a positive deflection (during positive pressure ventilation) (Figure 11.6). This method decreases interobserver variability and can also be utilized for measuring CVPs in ventilated patients. Knowledge of the patient's ratio of inspiratory time to expiratory time (I:E ratio) can also assist in understanding respirophasic changes in the wedge pressure (Figure 11.5).

The PAWP, even when measured carefully, may not always represent an adequate measurement of left ventricular preload. Conditions such as elevated abdominal pressure (e.g., intra-abdominal hypertension, active expiration), elevated set or occult PEEP (e.g., chronic obstructive pulmonary disease [COPD]), or abnormal myocardial compliance may lead to an erroneous overestimation of left ventricular (LV) preload and prompt diuresis or inadequate resuscitation.

Finally, it is important to be cognizant of the classic west zones of the lung. If the tip of the pulmonary artery catheter (PAC) is located in a nonperfused (zone 1) region of the lung, marked increases in the apparent wedge pressure during positive-pressure inspirations are noted and may not accurately represent left atrial pressure.

COMPLICATIONS

Pulmonary artery catheters can migrate distally. Under these circumstances, the pressure tracing on the monitor changes from a PA pressure tracing to one that resembles a persistently wedged catheter despite the balloon being deflated. When this occurs the catheter should be withdrawn

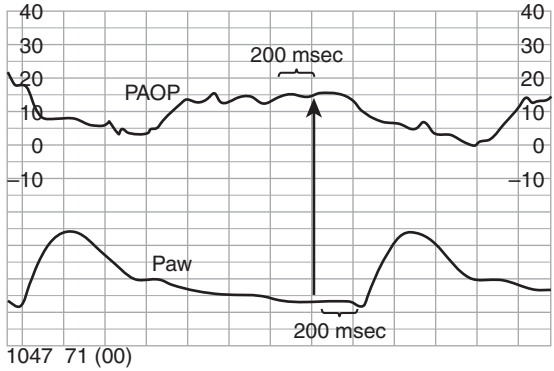


Figure 11.6 Strip-chart recording of a pulmonary artery occlusion pressure (*PAOP*) and airway pressure (*Paw*) waveform was obtained from a patient with acute respiratory distress syndrome who was receiving ventilatory support in the assist-control mode of mechanical ventilation. The waveforms demonstrate a fall in vascular pressure during the time that the ventilator is generating positive airway pressure, indicating active patient inspiratory efforts during each positive pressure breath. End-expiration was identified by drawing a vertical line 200 msec before the initial positive or negative Paw deflection of each breath. PAOP was measured by drawing a horizontal line through the visually weighted mean vascular pressure beginning at the end-expiratory time point, as identified above, and continuing backward another 200 msec. In this case, PAOP was recorded as 14 mm Hg. *(From Rizvi K, deBoisblanc BP, Truwit JD, et al: Effect of airway pressure display on interobserver agreement in the assessment of vascular pressures in patients with acute lung injury and acute respiratory distress syndrome. Crit Care Med 33:98-103, 2005, with permission.)*

until a PA pressure tracing returns. If unrecognized, this may result in a pulmonary infarction or pulmonary artery rupture if the balloon is inflated.

Lesser degrees of distal migration also may occur with persistence of PA pressure tracings on the monitor. Under these conditions, catastrophic PA rupture may also occur if the balloon is inflated with the full volume of air (1.5 mL). One should always watch the PA pressure tracing when inflating the balloon and stop introducing more air immediately if it changes to a wedged tracing or if any resistance is met. If there is any concern, the balloon should be deflated and the catheter should be withdrawn proximally until an identifiable pressure tracing is present. Other established risk factors for PA rupture include the presence of coagulopathy and pulmonary hypertension. As a result, some ICUs prohibit routine (e.g., every 4 hours) wedging of the PA catheter in patients with one or both of these factors. Changes in the PA diastolic pressure can often be tracked as a surrogate for changes in the PAWP.

The risk of catheter-associated infections has been reported to increase dramatically with time. Similar to central venous catheters, routine replacement of pulmonary artery catheters has not been shown to reduce complications. Infectious complications can be reduced by removing the catheter promptly when there is a change in appearance of the entrance site or when it is no longer deemed necessary. Insertion of a triple-lumen catheter through the diaphragm of the sheath after removal of a PA catheter is not a safe or sterile practice and should be discouraged.

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CHAPTER 12

Approach to Supportive Care and Noninvasive Bedside Monitoring

Warren Isakow ■ Jonathan E. Gottlieb

Patients are commonly admitted to the intensive care unit (ICU) for four principal reasons: (1) ICU level of monitoring, (2) intensive nursing care, (3) specialized procedures, and (4) therapies that carry special requirements or risk. On ICU admission, patients have certain needs related to their admitting diagnoses such as gastrointestinal hemorrhage, septic shock, or acute renal failure. In addition, all patients require special attention to several universal needs. Meeting these individual and common needs is the collective goal of ICU supportive care.

Considering a basic checklist of supportive care for every ICU patient is important for several reasons. First, in the rush to treat a critically ill patient's acute problems, one may overlook simple but important care. Second, serious illness invariably affects remote systems not involved in the primary pathophysiologic process. Third, treatment aimed at correcting one problem may create others. Supportive ICU care conforms to the general schema of admitting orders for any hospitalized patient (Table 12.1). In addition, it is helpful to systematically address possible needs for each organ system ("from head to foot"), including neurologic, ophthalmologic, otolaryngologic, integumentary, endocrine, metabolic, respiratory, cardiovascular, gastrointestinal, renal, musculoskeletal, and integumentary. In the head-injured patient, for example, failure to specifically address prevention of deep venous thrombosis, gastric stress ulceration, or skin injury may have serious consequences.

The value of formal checklists in the critical care setting has recently received much attention in the medical literature, with demonstrations of the significant impact of checklist use on central venous catheter infection rates and other outcomes.

Body Positioning

Most individuals admitted to the ICU are confined to bed for the initial part of their illness. The clinician must go far beyond the usual prescription of "bed rest" for the ICU patient, as the hospital bed becomes that patient's immediate and total physical environment. Bed confinement confers risks of aspiration, pressure ulcers of skin and soft tissue, musculoskeletal problems, abnormal cerebral perfusion, increased oxygen consumption, and basic discomfort. Far from being a simple matter of placing the patient in a comfortable position, positioning has become the subject of considerable study.

By default, most patients are initially placed in the supine position and turned regularly onto their sides to prevent both prolonged exposure (> 2 hours) of body protuberances to pressure and also atelectasis of dependent lung segments. Despite nearly universal support for the "2-hour benchmark," a study across 40 intensive care units documented that the mean time between turns approached 5 hours, and another investigator observed 2-hourly changes in position in only 3% of ICU patients over an 8-hour observational period.

Improved reliability of periodic turning partly explains the increasing use of rotational therapeutic beds. These devices perform timed alternating lateral positioning through sequential inflation

TABLE 12.1 ■ **Basic Orders for Patients Admitted to the ICU**

BASIC ORDERS	ICU CONSIDERATIONS
Diagnosis	Are there diagnosis-specific protocols or pathways? Do the patient's characteristics match admission criteria?
Condition	All but patients admitted for monitoring should be identified as "critical."
Allergies	Extremely important to inquire and document any drug allergies.
Activity	Consider careful and explicit rationale for restraints, special beds, positioning.
Vital signs	Each ICU has its own frequency of vital signs. Specify use of non-invasive monitors (e.g., pulse oximetry); list parameters for physician notification (e.g., call physician for heart rate > 120 or < 60).
Diet	Specify use of nasogastric or duodenal feeding tubes where appropriate; estimate caloric requirements; consider special electrolyte or fluid needs; maintain some enteral feeding for patients receiving hyperalimentation, unless contraindicated (Chapter 15). Use nutrition consultation and special hyperalimentation order sheets. Consider measuring nitrogen balance, where appropriate.
Diagnostic procedures	Will alert nursing staff to coordinate offsite transport or to prepare the equipment for bedside procedures.
Fluids	Pay attention to decreased, insensible water loss in ventilated patients (may gain up to 500 mL/24 h).
Special considerations	Eye protection for paralyzed patients; mouth care for intubated patients.
Preventive measures	Use subcutaneous heparin or pneumatic compression devices for deep venous thrombosis prophylaxis; use enteral feeding, sucralfate, proton pump inhibitor, or H_2 blocker for stress ulcer prophylaxis for patients in high-risk group (Box 12.1).
General medications	Assure adequate control of pain and anxiety (Chapter 5); write for a PRN (as needed) sedative for sleep (Chapter 44).
Special medications	Particular care should be given to drug interactions, impaired renal and hepatic clearance, and decreased blood flow in shock states (Chapter 17).

or other mechanical means. One large prospective randomized study and a meta-analysis identified decreased development of pneumonia with rotational therapy. Lateral positioning may improve oxygenation in patients with severe unilateral pneumonia, who often respond favorably when the "good" (nonconsolidated) lung is "down" (in the dependent position). The rationale for this improved oxygenation is that gravity favors blood flow to the dependent, uninvolved lung and increases pulmonary blood flow to the better-ventilated alveoli. This effect of gravity on pulmonary blood flow improves ventilation/perfusion matching (fewer alveoli with low ventilation/perfusion) and decreases shunting through fluid-filled alveoli (whose ventilation/perfusion = 0), and both changes improve oxygenation. In evaluating a critically ill patient, it is important to interpret alterations in oxygenation in the context of any positional changes that may affect ventilation-perfusion matching.

Some centers treat patients with acute respiratory distress syndrome (ARDS) by periodic turning to and from the prone position to improve oxygenation (see Chapter 73). Extensively investigated, prone positioning consistently produces transient but significant improvement in oxygenation indices in many patients, but without conferring survival or other outcome benefits.

In the case of severe hemoptysis (usually > 300 mL/24 hours) from a unilateral lesion, the opposite recommendation applies: turn patients so that the bleeding lung is in the dependent position ("bad" lung down). In this circumstance, gravity deters blood from spilling across the midline to the contralateral, nonhemorrhaging lung. This maneuver may be lifesaving in an emergent situation (see Chapter 79).

For many years, patients were routinely placed horizontally (flat) in the supine position for ease of care. This fully recumbent position facilitated the calibration and zeroing of transducers, routine nursing care, and the preventon of falls. Unfortunately, supine positioning increases the risk of aspiration (as demonstrated by tracer studies), nosocomial pneumonia, and mortality. For this reason, keeping the head of the bed elevated 30 to 45 degrees, especially in mechanically ventilated patients or those receiving gastric tube feedings, has been recommended in the ICU. The Centers for Medicaid and Medicare Services (CMS) has considered making maintaining head of bed elevation > 30 degrees reportable as a quality process measure, along with ventilator-associated pneumonia (VAP) as an outcome measure. Important factors make VAP an unreliable outcome measure, although head-of-bed elevation is becoming widespread.

Some patients with neurologic disease may benefit from elevating the head of the bed to 30 degrees, which reduces intracranial pressure up to 10 mmHg. However, elevating the patient's upper body may create extra shear stress exposure to the skin of the back, sacrum, and lower extremities, increasing the risk of skin injury and breakdown (Chapter 42).

Any special requirements for body positioning must be discussed among the entire ICU care team. The documented difficulty of maintaining compliance with frequent position changes, risk of back and other stress injury to the clinician, and potential danger of malposition or disconnection of catheters during movement all summate to require well-planned and meticulously implemented position changes by the multidisciplinary team. Unfortunately, because of their spectrum and the severity of their critical illness, sicker patients receive less frequent position changes. Thus, formal team communication, visual cues, and feedback of performance data all enhance the reliability of positioning among other standard ICU work.

Skin Care (see also Chapter 42)

RISK FACTORS FOR SKIN INJURIES

The skin is the first line of the body's defense against the external environment, but multiple factors conspire to violate these defenses in the ICU patient. Whether chronically ill and debilitated, or acutely and catastrophically ill, the ICU patient may have poor nutrition, limited anabolic capacity, or both. The skin becomes fragile, unable to resist normal assaults, and lacks the capacity to heal. Low albumin, decreased subcutaneous fat, edema, obesity, diabetes, incontinence, extreme age, immobility, and impaired immune responses all increase susceptibility of the skin to injury. Chronic corticosteroids exacerbate this problem. Shock and other hypoperfusion states decrease blood flow to the skin, also impairing normal healing. In addition, the skin is subject to an array of physical trauma in the ICU. These traumas include perforation by needles and catheters, shear stress during bed transfers and repositionings, abrasions resulting from dressing adhesives, and pressure from orthopedic devices and other surfaces contacting the skin.

The first step is minimizing physical trauma to the skin when performing procedures and applying or removing dressings. Give attention to improving the peripheral perfusion and nutritional status of the patient. In general, turn sedated patients (with or without paralysis) every 2 hours to avoid the development of pressure ulcers.

SPECIFIC INTEGUMENTARY CONDITIONS

Wounds

Generally, dress wounds with sterile dry dressings for 24 to 48 hours after surgery, until drainage ceases. Subsequently, change dressings for convenience to protect any exposed surface and sutures and to observe the wound for signs of redness, swelling, or purulence. Contaminated wounds are generally managed "open"—that is, without primary closure. Wet-to-dry dressings may be

applied using normal saline or other sterile solutions; routine use of Dakin's solution, povidone-iodine, and other antiseptics may impede wound healing.

Stomas

Stomal mucosa should always be warm and pink; duskiness signals poor perfusion. Usually, an enterostomal therapist manages initial stoma care. Frame stomas with a ring that provides a ¼-inch circumferential margin. Stomas with no signs of redness, ischemia, purulence, or breakdown need only infrequent dressing changes.

Drains

Drains must be left open and require frequent changes of dry dressings if the drain output is easily absorbed. Collect larger volume drainage into an ostomy bag or special collecting bag, and frequently change the bag to prevent overflow or contamination and to measure output.

Fistulas

Fistulas are some of the most difficult wounds to manage, particularly in the perineal area. They may be kept clean with frequent changes of dry dressings and observed for signs of abscess formation or skin breakdown. Preventing skin breakdown may be impossible with copious drainage from cutaneous fistulas, particularly in critically ill patients.

Pressure Ulcers

Pressure ulcers occur from immobility or appliances in contact with the skin (see Table 42.1, Chapter 42). The Agency for Health Care Policy and Research has developed comprehensive guidelines for the problem of pressure ulcers. Prevention and treatment of pressure ulcers are described in Chapter 42.

Superficial Fungal Infections

Superficial fungal infections frequently involve *Candida* or *Torulopsis* and may be treated with a topical Mycostatin or clotrimazole cream.

SPECIAL CARE BEDS

Because of the frequency of pressure ulcers and other skin injury in the ICU, particular attention has been paid to the interface between patient and bed, leading to a number of specialized approaches (see Box 42.1, Chapter 42).

A *mattress overlay* consists of an inexpensive (several hundred dollars) surface to distribute pressure across a wider skin area. Remember that the usual, colorful but thin "egg crate" overlay mattress inadequately protects body protuberances against pressure injury. These overlay mattresses lack sufficient height to horizontally distribute enough pressure from the body's weight away from the protuberance to prevent skin ischemia, which may occur as quickly as 2 hours.

A second approach combines a special pressure-reducing surface with an automatic, periodic, side-to-side rotation of the bed to alternate areas of the skin subjected to pressure. This type of bed has been used successfully for patients in traction, with spinal cord injury, or placed in a prone position (as an adjunctive treatment for ARDS).

In a third approach, individual mattress segments are inflated either concurrently or sequentially to distribute pressure over a wider surface area (low air-loss bed). This sequential inflation and deflation process automatically rotates the points of maximal contact with the patient's skin.

A fourth approach employs air-fluidized silicon beads, covered by a semipermeable material. This bed produces a "floating" sensation and virtually eliminates concentrated pressure points on

the patient's skin. In addition, the constant airflow keeps the skin dry and augments insensible water loss. One drawback is this device requires the patient to be fully recumbent. Should the need for cardiopulmonary resuscitation arise, it is imperative to shut off airflow in order to provide a firm horizontal surface.

Patients at high risk for skin breakdown benefit from one of these specialized approaches. Some studies demonstrate cost savings and improved outcome with use of the low air-loss or air-fluidized approach in high-risk ICU patients, compared with a standard mattress. Other studies, however, demonstrate increased costs without significant improvements in outcome.

Malnourished ICU patients with diabetes, with poor skin perfusion subjected to multiple dressing changes and skin punctures, obesity, or fecal incontinence have high risk for skin ischemia and pressure ulcers. Place these patients on an appropriate mattress overlay or low air-loss or air-fluidized bed to prevent serious skin breakdown. The selection of the specific product depends on local hospital and clinical practice as well as on individualized patient assessment. Because these specialty beds are effective but very expensive, appropriate use includes restricted utilization to those most high-risk patients (see Chapter 42).

Aseptic Technique

In general, nosocomial infection is the major cause of death in critically ill patients. Most patients with malignancy who die in the ICU do not primarily succumb to their cancer but rather the infectious complications. Therefore, observing simple but effective infection control measures is of paramount importance (see Chapter 14).

The most common and flagrant violation of aseptic technique involves handwashing. Numerous studies demonstrate resistant organisms are carried on the hands of caregivers from patient to patient and, in some ICUs, cause epidemics of multiple drug–resistant pathogens with high mortality. Handwashing with a germicidal solution is imperative to prevent the spread of organisms. Wash hands before and after contact with every ICU patient.

Wear masks and gloves for every sterile procedure performed, including thoracentesis, placement of arterial and central venous catheters, and paracentesis. In addition, donning sterile gowns during central venous and pulmonary artery catheter placement facilitates the manipulation of equipment without losing asepsis and reduces bloodstream infections. Clean the skin with alcohol and chlorhexidine, beginning at the center and gradually increasing the diameter of the cleansed area using a circular motion. Dispose of the gloves after completing the episode of patient contact and before answering the telephone or writing in the chart.

The increasing incidence of *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and other resistant organisms in the ICU mandates compliance with these infection control practices, as well as adherence to specific hospital policies for isolation of ICU patients infected or colonized with these resistant organisms.

Non-invasive Monitoring

Most ICU monitoring is non-invasive, as it does not violate the normal defense mechanisms of the patient. For example, *heart rate* can readily be taken from the surface electrocardiogram electrodes, oscillometric blood pressure cuff, or pulse oximetry waveform. Non-invasive monitoring may reflect the adequacy of stroke volume, depth of sedation, and analgesia, or the presence of pneumothorax or other problems.

Respiratory rate can be determined through changes in thoracic electrical impedance, as the distance between standard electrocardiogram electrodes changes during respiration, or alternatively by pressure or flow changes detected in the mechanical ventilator circuit. Both of these

methods, however, may underestimate or overestimate the actual respiratory rate, requiring observation of the patient, chest wall excursions, and inspiratory efforts to confirm these data.

Non-invasive determination of *temperature* may significantly underestimate fever. Tympanic membrane and axillary measurements may result in errors of 1° to 2° C when compared with simultaneous core or rectal temperature. Therefore, always correct tympanic membrane measurements for any discrepancy to core temperature readings, and avoid axillary measurements altogether in patients with shock or sepsis.

When noting discrepancies between arterial catheter and cuff measurements of blood pressure, clinicians frequently mistrust the non-invasive cuff method. However, peripheral vasoconstriction, catheter resonance, damping, and other factors may produce overestimation or underestimation of blood pressure by the catheter-transducer method, especially if a peripheral artery is cannulated. In the presence of shock or an abnormal arterial waveform, cuff blood pressure measurement by the oscillometric or ultrasonographic method may be preferable.

Non-invasive determination of arterial blood pH, Pao_2, and $Paco_2$ remains an elusive goal of critical care monitoring. *Pulse oximetry* is a valuable addition to arterial blood sampling in the ICU, although it remains an imperfect replacement in the operating suite. Pulse oximetry depends on the transmission and absorbance by hemoglobin of two or three wavelengths of light through a capillary bed, usually in the fingertip or earlobe. Because hemoglobin absorbs light in relation to its saturation with oxygen, a computer can calculate hemoglobin saturation continuously. Peripheral vasoconstriction is an important cause of inaccuracy of pulse oximetry. Importantly, some patients, usually those with respiratory failure, show poor correlation between arterial blood saturation measured directly by a laboratory co-oximeter and saturation as measured by pulse oximetry. If such discrepancy is documented, do not rely on the absolute values of pulse oximetry to guide treatment decisions but rather use changes in values to identify potential problems. One need also remember that oxyhemoglobin saturation by pulse oximetry says nothing about arterial pH or $Paco_2$.

Clinicians have attempted to supplement pulse oximetry to non-invasively assess adequacy of ventilation by monitoring end-tidal Pco_2 with *capnography*. Despite initial enthusiasm, capnography in patients on ventilators has limited value. Most ICU patients receiving mechanical ventilation have intrinsic lung or airway disease, with abnormal patterns of expired CO_2 making both initial measurement and subsequent interpretation of "end-tidal" Pco_2 problematic. The same abnormal result may arise from hypoventilation, tracheal secretions, bronchospasm, pulmonary edema, or a number of other frequent complications in ICU patients, as well as technical difficulties in making the measurement. Capnography of end-tidal Pco_2 may offer utility in monitoring patients on ventilators who are clinically stable and free of intrinsic lung disease, such as those with respiratory failure caused by neuromuscular weakness.

Invasive Catheters

See Chapter 11 for a discussion of intravascular catheters.

URINARY CATHETERS

Urinary catheters are frequently used to indirectly monitor renal perfusion and assist in fluid balance. Unfortunately, they also provide a ready source of colonization and potential infection of the bladder and upper urinary tract. Traction on the catheter may produce urethral injury, particularly in patients with hemostatic disorders. In the absence of a local complication, there is no compelling reason to change the urinary catheter in an ICU patient. It should be removed as soon as the patient can assist with urination. Studies indicate that many patients in ICUs continue with these catheters beyond the appropriate time for removal.

RECTAL TUBES

Rectal tubes may prevent skin breakdown and improve the ability of nurses and others to care for patients with profuse diarrhea. However, mucosal necrosis and bleeding may occur because of the high pressure needed to maintain a rectal catheter in place. For this reason, many deflate the balloon every 4 hours for 0.5 hour to prevent these complications. Some ICUs avoid rectal tubes completely because of these intrinsic risks in critically ill patients and use rectal "trumpets" instead.

NASOGASTRIC TUBES

Nasogastric tubes (NG) are frequently used in intubated patients to prevent gastric distention, ascertain gastric pH, and deliver nutrition and medications. A common complication occurs when the tube is flexed upward (over the patient's forehead) to clear it from the patient's mouth, neck, and thorax. Avoid this upward angulation, which may produce nasal necrosis. Instead, allow the tube to follow a natural downward loop and curve laterally near the ear, where it may be redirected without causing undue pressure on the nose. When used primarily for feeding, small-diameter, soft feeding tubes should be substituted for NG tubes. Verification of correct placement of all feeding tubes should be performed using radiography, carbon dioxide detection, or direct inspection to prevent inadvertent bronchial or pleural instillation of feedings. The presence of a nasoenteric tube also confers a risk of sinusitis and promotes gastroesophageal reflux by violating the gastroesophageal sphincter.

TRACHEOSTOMY TUBES

Tracheostomy tubes are most frequently secured with adhesive tape or umbilical ties. The tape may be double-faced around the back of the neck to minimize irritation and discomfort. One finger should fit between the adhesive tape or umbilical tie and the neck to prevent excoriation of the skin. Newer Velcro and fabric fasteners have been used, but some find these devices less reliable. After initial tracheostomy, the fistula (track) becomes established over a period of time (usually about 7 days), after which time a member of the surgical team that performed the procedure should also do the first change of the tracheostomy tube (external cannula). After this initial tracheostomy tube change, following maturation of the stoma and track, the ICU team can safely perform subsequent changes.

ENDOTRACHEAL TUBES

Endotracheal tubes represent a major source of bacterial colonization of the tracheobronchial tree. The endotracheal tube circumvents normal defense mechanisms, promoting development of a biofilm, facilitating continuous aspiration of secretions, and bypassing the glottis to impair the cough reflex. Several strategies have been attempted to modify this risk factor, including selective decontamination, utilizing silver-impregnated tubes, continuous aspiration of subglottic secretions. Each yields some measured benefits, but none favorably impacts mortality, length of ICU stay, or duration of mechanical ventilation. Furthermore, the marginal cost of these interventions exceeds less costly measures, such as head of bed elevation in preventing ventilator-associated pneumonia.

Moreover, traction on the endotracheal tube may produce injury or necrosis to the oral mucosa, tongue, and angles of the lips. Therefore, reposition the tube at a minimum every 24 hours, preferably alternating sides of the mouth. Provide regular mouth care, inspecting for signs of ulceration, necrosis, or injury. Once a chest radiograph has verified correct tube position, distance markings on the tube at the level of the maxillary teeth can document tube positions after repositioning.

Eye Care

In sedated, paralyzed, or otherwise immobile patients, particularly those connected to a mechanical ventilator, there is an increased risk of injury or infection to the eye. About one third of critical care patients may develop exposure keratopathy.

Decreased tear protection resulting in corneal drying and ulceration may occur without appropriate interventions. Therefore, regularly apply an ointment or liquid wetting agent (e.g., Lacri-Lube) to prevent drying of the cornea. Alternatively, a meta-analysis suggested that use of a moisture chamber was superior to wetting agents in preventing exposure keratopathy.

Take care to prevent eye injury from falling instruments, ventilator or other tubing, or pooling secretions. If needed, lightly tape simple gauze pads in place to keep eyelids closed, or use a moisture chamber. Routinely examine the eyes for signs of infection or subconjunctival edema, and request ophthalmic consultation for any evidence of injury. Subconjunctival edema may result from high inspiratory ventilator pressures and does not require any specific treatment.

Stress Ulcer Prophylaxis

In the first decades of ICU care, acute gastric stress ulceration leading to uncontrollable gastrointestinal hemorrhage was an all-too-frequent catastrophic complication of critical illness. Indeed, this cause of massive bleeding and associated emergent surgery significantly contributed to ICU morbidity and mortality. However, many studies performed in the 1970s and 1980s demonstrated the benefit of prophylactic antacid or H_2-blocker administration to prevent the development of acute stress ulceration. Additional experience revealed several alternative therapies and reduced the frequency of acute stress ulceration and bleeding, including the administration of sucralfate, tube feeding, and proton pump inhibitors.

After wide implementation of effective stress ulcer prevention, attention shifted to the potential complications. Alkalization increases bacterial colonization of the stomach, which may increase the incidence of nosocomial pneumonia in mechanically ventilated patients. Sucralfate must be given by NG tube in the intubated and ventilated patient, thereby risking sinusitis, nasal trauma, and gastroesophageal reflux (see the discussion presented earlier), and a meta-analysis suggested sucralfate to be inferior to acid suppression. Clinical studies demonstrate equivalence of proton pump inhibitors compared to H_2 receptor antagonists.

Glucose Control

Hyperglycemia is a known complication of critical care and carries an increased risk of infection, organ failure, and mortality. The early 2000s witnessed a tremendous increase in the study of glucose control, our knowledge of how to treat hyperglycemia, and the associated benefits and consequences. Tight glucose control improves function and decreases complications in the ambulatory diabetic. However, initial enthusiasm for tight glucose control in the critically ill has been substantially tempered by the inability to consistently demonstrate benefits and the identification of potentially harmful hypoglycemia (< 60 mg/dL). Consequently, many centers no longer embrace tight glucose control for all critically ill patients.

Tight glucose control may not confer easily observed benefits for several reasons. Our ability to manage hyperglycemia in general has improved with better point-of-care testing, introduction of insulin analogues, and deeper understanding of the pathophysiology of hyperglycemia. In addition, the investigation of tight glucose protocols in critically ill patients generally utilized control groups with mean glucose concentrations well below 200 mg/dL and small differences between intervention and control groups, generally in the 30 mg/dL range. Currently, it appears prudent to target glucose concentrations below 150 mg/dL while avoiding hypoglycemia.

Prophylaxis for Thromboembolism

Critically ill patients are at substantial risk for venous thromboembolism (Chapter 77), and deep venous thrombosis (DVT) prophylaxis effectively reduces morbidity and mortality (Box 12.1). Therefore, consider all critically ill patients, particularly those who are mechanically ventilated or immobilized, as candidates for DVT prophylaxis.

The two most common methods utilize subcutaneous heparin in a dose of 5000 units every 8 hours or pneumatic compression devices. The latter are usually offered for patients who initially present with active bleeding, contraindications to heparin, spinal cord injury, or other neurosurgical conditions.

In patients with major trauma, the standard subcutaneous heparin dose may be inadequate. One study of this population revealed this regimen of heparin showed no decrease in the incidence of DVT detected by ultrasonography. Placement of prophylactic inferior vena cava filters in trauma patients reduced the occurrence of fatal pulmonary embolism, and approximately 25% of trauma centers routinely use these filters in such patients.

Some experts treat spinal cord–injured patients first with an initial period of observation using compression boots, followed by adjusted-dose intravenous heparin to achieve measurable prolongation of the partial thromboplastin time in a therapeutic range. Others suggest a decreased incidence of venous thromboembolism (VTE) in spinal cord injury patients following the initial 6 months after injury. Although controversy remains about the most effective VTE prophylaxis in critically ill subgroups, general consensus exists that critically ill patients benefit from pharmacologic prophylaxis of VTE and from pneumatic compression devices if pharmacologic treatment is unfeasible.

Phlebotomy and Erythropoietin

The mere presence of a patient in the ICU risks excessive and unnecessary phlebotomies. Use of central venous catheters and arterial catheters increases the convenience with which large volumes of blood may be sampled from critically ill patients. Indeed, one study noted that for routine laboratory collections, blood drawn was 45 times in excess of the required volume. Another study examined phlebotomies in two groups of patients with similar severity of illness but only one group having arterial catheters in place. The group with arterial catheters experienced a 30% greater number of blood tests and blood draws, with a 44% greater amount of blood volume removed.

The simplest and most responsible solution to iatrogenic anemia is to evaluate the need for each laboratory test. Daily electrolyte determinations, complete blood counts, and other routine

BOX 12.1 ■ Guidelines for Prophylaxis of Deep Venous Thrombosis in ICU Patients

1. Consider all immobile, heavily sedated, or mechanically ventilated patients as candidates for deep venous thrombosis prophylaxis.
2. Begin subcutaneous heparin 5000 units q12h as prophylaxis (unless contraindicated).
3. In patients with contraindications for receiving heparin, institute pneumatic compression devices. Before using such devices in previously immobile patients, check lower extremities for presence of proximal clot by Doppler ultrasound or impedance plethysmography (Chapter 77).
4. For special high-risk groups, such as spinal cord–injured patients or trauma patients (lung ventilator dependence, multiple lower extremity fractures, major abdominal or pelvic venous injury or pelvic and lower extremity fractures), consider prophylactic IVC filters followed by systemic anticoagulation.

IVC, inferior vena cava.

studies are ordered far more frequently than required for patient management. Other approaches to reduce iatrogenic anemia include the use of blood-conserving devices to minimize the discarded blood volume (up to 50% of the total blood withdrawn) and pediatric specimen tubes.

Recombinant erythropoietin has been studied in critically ill patients, as a strategy to reduce the number of transfusions. However, erythropoietin does not reduce the number of patients who receive red cell transfusions or the absolute number of packed red cell transfusions. Erythropoietin use has been associated with higher rates of clinically relevant thrombosis and should not be routinely employed for anemic patients in the ICU.

An annotated bibliography can be found at www.expertconsult.com.

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Corwin HL, Gettinger A, Fabian TC, et al: Efficacy and safety of epoetin alfa in critically ill patients. N Engl J Med 357:965-976, 2007.

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Lyder C: Pressure ulcer prevention and management. JAMA 289:223-226, 2003.

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Using radioactive tracer, these authors suggested that the semirecumbent position protects from pulmonary aspiration of gastric contents but not from gastroesophageal reflux or oropharyngeal colonization.

Pronovost P, Needham D, Berenholtz S, et al: An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 355:2725-2732, 2006.

This is a large collaborative cohort study in 103 ICUs in Michigan. A simple and inexpensive intervention (hand washing, full barrier precautions during insertion, skin cleansing with chlorhexidine, avoiding femoral lines, and early removal of catheters) reduced the rate of catheter-related bloodstream infections from 2.7 per 1000 catheter days

to 0 within 3 months. The benefit of the intervention was sustained at 18 months with a 66% reduction in the rate of catheter-related infections.

Raghavan M, Marik PE: Anemia, allogeneic blood transfusion and immunomodulation in the critically ill. Chest 127:295-307, 2005.

This is an excellent review of the immunomodulatory effect of blood transfusions and the implications of transfusion practice for critically ill patients.

Torres A, Serra-Batlles J, Ros E, et al: Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. Ann Intern Med 116:540-543, 1992.

These authors found one third the aspirated radioactivity at one half hour and one tenth the radioactivity at 5 hours with the semirecumbent position compared to the supine position. In addition, they noted isolation of concordant organisms from the stomach, pharynx, and endobronchial samples in 32% of semirecumbent patients and 68% of supine patients.

CHAPTER 13

Management of the Critical Care Patient

Joshua B. Kayser ■ Paul N. Lanken

Day-to-day management of critically ill patients in intensive care units (ICUs) can be challenging. Not only are the clinical data of many ICU patients complex and changing frequently, but their medical records are often voluminous. Furthermore, their clinical status often changes rapidly and unexpectedly. Adding to these challenges is that specific etiologies of acute events that resulted in ICU admission may remain unknown for days, if not weeks or longer, after admission. As such, short- and long-term prognoses may likewise remain unclear along with the family's or patient's goals of care. Patient- and family-centered (Chapter 104) day-to-day management depends on effective communication, handoffs ("handovers"), and other collaborative practices that, in turn, depend on daily multidisciplinary rounds (Chapter 103). This chapter describes the principles and practices of successful day-to-day management of ICU patients. It highlights the key information that ICU clinicians should obtain and assess to maximize efficiency and accuracy in day-to-day patient management.

A Primer on Data Collection

In the modern ICU, large amounts of patient data are generated on a daily basis and need timely review and evaluation. These include not only the data at hand but also what may be referred to as *meta-data*—that is, trends or other changes in today's data compared to data from yesterday and prior days and patterns of changes in the current data compared to prior patterns (Box 13.1). As a result, ICU clinicians are required to assimilate and codify an extraordinary number of details for each of their ICU patients in order to make decisions and organize a plan of care.

Three processes are involved in memory: encoding, storage, and retrieval. *Encoding* refers to how something is processed for memory in the brain. Once it has been encoded, it can then be *stored* in the form of a short-term or long-term memory. *Retrieval* is the process of getting information from a memory. Most ICU data are stored in a subdivision of the short-term memory, termed the working memory, for quick processing. However, humans can only process a limited number of details (about seven) for short intervals in the working memory.

However, a typical ICU clinician is required to be familiar with many more than seven details daily for each ICU patient. This presents an intrinsic challenge to successful processing of ICU data on rounds and day-to-day management of critically ill patients, especially when the ICU clinician must also follow trends or evolving patterns of changes in data. Additionally, the data are often subject to irregular sampling, measurement error, and interpretation error, as well as the inherent bias of the individual clinician in terms of what to believe and base decisions on. Accuracy and consistency can thus be difficult to achieve.

Additional online-only material indicated by icon.

BOX 13.1 ■ Essential Data in the Day-to-Day Management of the ICU Patient

History, Interval

Review overnight events with nursing and covering providers, including abnormalities on ECG telemetry, and telemedicine providers' report, if applicable
Review chart for updated consults or progress notes
Medication reconciliation

Physical Exam

Vital signs
Mental status, including level of pain (see Figure 5.1 and Table 5.1, Chapter 5), sedation (RASS score) (Table 5.2, Chapter 5) and presence or absence of delirium (CAM-ICU) (Figure 37.1, Chapter 37)
Focused physical examination

Bedside Data

Assessment of catheters and tubes
Mechanical ventilator settings
Intravenous infusions (including sedatives and vasopressors and their trends or past 24 hours)

Labs and Other Studies

Common Laboratory Tests

Basic metabolic panel (+/– liver function tests)
CBC
Coagulation studies
Arterial/venous blood gases
Blood and other cultures

Common Radiographic Studies

Chest and other radiographs
CT scans

CBC, complete blood count; CT, computed tomography; RASS, Richmond Agitation-Sedation Scale; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit.

Monitoring of Overnight Events and Patient Assessment

In this age of medical care, information is passed from clinician to clinician with greater frequency than in the past (e.g., so-called handoffs or handovers). It is therefore crucial that a detailed account of overnight events be given at the beginning of each day. A recommended approach is for the daytime ICU clinicians to discuss major events from the previous night with the physicians and nurses who cover the nighttime shift, followed by a review of notes and documentation. ICU nurses spend the largest percentage of time at the bedside of their patients, and are thus an invaluable resource. Input from clinicians based on telemedicine units that remotely monitor certain ICU patients (Chapter 111) can also be an important source of information about the nighttime events.

The daily assessment proceeds with systematic review of vital signs and fluid balance (i.e., intake and output—I's and O's) over the previous 24 hours. In the ICU, vital signs include temperature, blood pressure, pulse, respirations, oxygen saturation (by pulse oximetry), and pain and other important signs and symptoms (e.g., level of sedation and presence of delirium).

In evaluating the patient's temperature curve, awareness of both hyperthermic and hypothermic episodes can provide useful information about infectious and inflammatory conditions in addition to common complications of ICU stays such as atelectasis and drug reactions.

Blood pressure is of vital importance to maintain normal body homeostasis. Adequate blood pressure is a key component in enabling the body to successfully deliver oxygen to the tissue and cellular level. Assessment of blood pressure should include both a review of systolic and diastolic pressures as well as the mean arterial pressure, which can serve as an indirect assessment of organ perfusion pressure.

Review of the patient's pulse should include both a quantitative assessment of heart rate as well as a qualitative assessment of rhythm. Additionally, it is important to review the alarm history on the telemetry monitor to diagnose any arrhythmias that may have occurred over the interval of interest.

Assessment of respiratory status and arterial oxygen saturation should include both breathing rate and pattern. Awareness of abnormal rates can be useful to diagnose increased work of breathing, which may subsequently lead to respiratory failure, or very slow rates, which may result from oversedation with respiratory depressant medications. Unusual patterns of respirations, such as Cheyne-Stokes or Kussmaul breathing or episodes of obstructive apneas, can also be valuable in diagnosing a patient's pathology.

Patients with respiratory failure who require mechanical ventilation should have their ventilator mode and relevant settings reviewed as well as serial arterial blood gases (ABGs) to assess acid base status, ventilation, and oxygenation. The latter includes assessing how closely the pulse oximetry readings of O_2 saturation are to the calculated or measured O_2 saturation by ABGs or co-oximetry, respectively. In association with respirations and O_2 saturations and ABGs, ventilator settings and functions should be reviewed at the bedside, including tidal volume (total and mL/kg predicted body weight [PBW], Appendix E), airway pressures (peak and plateau), minute ventilation, and evidence of auto positive end expiratory pressure (auto-PEEP) (see Chapters 2, 3, and 47).

Because of its importance for patient- and family-centered care, some argue that pain measurement (e.g., Figure 5.1 in Chapter 5 and Figure 87.1 in Chapter 87) should be regarded and treated as the "fifth vital sign" in ICU patients. The same could be argued regarding the patient's level of consciousness (e.g., level of sedation or agitation and the presence and severity of delirium). Regarding the latter, it is recommended that both the goal of sedative therapy and actual level of sedation achieved be communicated by a standard method, such as by using the Richmond Agitation-Sedation Scale (RASS) (Chapter 5). Likewise, a standard method of evaluating for the presence of delirium (e.g., the Confusion Assessment Method for Intensive Care Unit [CAM-ICU]) is preferred over less systematic methods.

Lastly, volume status (intravascular and total body fluid volumes) should be reviewed. Assessment of total intake and output, including a breakdown in type of intake (e.g., parenteral versus enteral) and output (urine, stool, drains, and tubes) can help clarify the significance of imbalances between "ins" and "outs." Urine output, in particular, is a simple way to assess for adequate organ perfusion (with usual threshold of adequate urine output being 0.5 mL/kg PBW/h). If patients have indwelling central catheters, notation of accurate measurements of central venous pressure (CVP) or pulmonary arterial wedge pressure (PAWP) can aid in the assessment of volume status.

Once the assessment of vital signs is complete, providers should examine the patient and talk with the patient and family members, if present (Chapter 104). At a minimum, one should perform a focused physical exam, including breath and heart sounds, mental status, and other neurologic signs, and inquire about the presence and intensity of pain, dyspnea, and other symptoms. When doing one's physical exam, one should carefully evaluate the skin to measure skin turgor; identify new pressure ulcers (Chapter 42), ecchymoses, or rashes (Chapter 43); assess temperature and capillary refill time in all extremities; and look for signs of infection at the insertion site of medical devices (Chapters 11 and 14). A mental status exam should be tailored to the individual patient, with either a qualitative assessment (alert, delirious, somnolent, obtunded, etc.) or a quantitative

assessment, such as the Glasgow Coma Scale (GCS) (Chapter 99), a sedation scale (e.g., RASS) (Chapter 5), or a delirium assessment (e.g., CAM-ICU) (Chapter 37).

A review of the ICU flow sheet (paper or electronic) can be helpful for assessing changes in clinical status of patients over the past 24 hours or longer as documented by the patient's nurses and respiratory therapists. Likewise, a review of the medical record (paper or electronic) for results of diagnostic tests in the past 24 hours as well as notes and recommendations by consultants, house staff, or other members of the ICU clinical team is recommended to round out the daily picture.

Medication Reconciliation and Nutritional Management

Examination of intravenous (IV) fluids and drugs that are being administered as continous IV infusions ("drips") and other medications is an essential part of the daily patient assessment. Common IV drips in an ICU setting include IV fluids, vasopressors, sedatives, analgesics, and antimicrobials. Pertinent information about IV drips includes the type and rate, changes over the past 24 hours or longer, as well as whether an IV drug is being administered continuously or by bolus. When assessing vasopressors, it is important to note any trends of dosage changes that may reflect a change in the patient's hemodynamic status. For patients on sedation, awareness of whether patients are on continuous infusions or bolus or if they receive a daily sedation interruption (i.e., a spontaneous awakening trial SAT, see Chapter 5) and its results are key components of the assessment of mental status, as sedation can adversely impact a patient's degree of alertness and cognition (see Chapter 36).

Antimicrobials should be reviewed in a systematic manner to avoid overutilization, which can result in antimicrobial resistance. When possible, a daily therapeutic plan should exist for each antimicrobial, including knowledge of the rationale for its use, the current number of days of therapy, and the planned number of days of treatment.

All medication orders should be reviewed daily, and any medications that are judged to be no longer necessary should be discontinued. Lastly, knowledge of other medications should include awareness of the dose and frequency as well as an assessment of administration (e.g., being administered, and if not, why being held) and awareness of potential drug side effects and interactions.

As with medications, the patient's current nutritional support should be reviewed in terms of type (Chapter 15), route of administration (Chapter 16), and whether or not it's at the nutritional goal as recommended by nutritional consultants. How the patient is tolerating the current level of nutritional support (e.g., presence of gastric residuals, abdominal distension and discomfort, and presence and type of stool) is an important element to keep on top of as well as whether the nutritional therapy is having its desired effect in terms of the patient's body weight and malnutrition indices (e.g., albumin and prealbumin) starting to trend in the appropriate directions of improved nutrition status (Chapter 15).

Laboratory Data

Critically ill patients routinely have an enormous amount of laboratory data. First, as a general imperative for all hospitalized patients, one should not order a laboratory study ("lab") if it is not needed. Just because patients are in the ICU doesn't necessarily mean they must have all or even most of their labs drawn daily.

Commonly, labs fall into one of three categories: metabolic, cellular, or coagulation. The most common *metabolic* studies include the basic metabolic panel (BMP) or "panel 7," which includes the serum sodium (Na^+), potassium (K^+), chloride (Cl^-), and bicarbonate (CO_2^-) as well as serum blood urea nitrogen (BUN), creatinine (Cr), and glucose (Glu). The complete or comprehensive metabolic panel (CMP) includes BMP elements plus serum calcium (Ca^+),

albumin (Alb^-), phosphate (P), and liver function tests (LFTs). Assessment of electrolytes is useful to review water and acid/base balance, renal function, and glycemic control. LFTs and albumin aid in evaluating hepatic function and the patient's nutritional status.

The *cellular* test most commonly ordered is the complete blood count (CBC), which allows for assessment of the white blood cell (WBC), hemoglobin and hematocrit (H&H or Hgb & Hct), and platelet (Plt) count. A review of the WBC should include not only total WBC count (leukocytosis or leukopenia) but notation of type of circulating WBC (polymorphoneutrophils [PMNs or "polys"], immature PMNs or bands, lymphocytes, etc.). A decrease in H&H can help to explain subjective dyspnea, pallor, new blood loss, or derangements in oxygen delivery. Finally, a review of the platelet count and its trend from ICU admission can help to explain new bleeding or ecchymoses or signs of a drug-induced thrombocytopenia (Chapter 45).

Coagulation studies most commonly involve measurement of prothrombin time (PT/INR) and partial thromboplastin time (PTT), standard measurements of extrinsic and intrinsic clotting function.

Other labs may prove helpful in certain clinical circumstances. These include lactic acid levels and central venous assessments of oxygen saturation (Scv_{O2}), both of which relate to how well tissues are oxygenated and perfused, especially in shock states (see Chapters 8, 9, and 10), as well as microbiologic data. When reviewing microbiologic data, it is essential to be aware of the source and date of the lab as well as results, including culture and sensitivities. As an example, if a patient with a fever underwent blood cultures, the provider should know the site of the culture (e.g., peripheral right arm), the organism (e.g., *Staphylococcus aureus*), and the sensitivities (e.g., pan-resistant except to vancomycin). As described in Chapter 14, one should avoid drawing blood cultures through an indwelling catheter because such blood cultures have high false-positive rates (unless the cultures are taken when the catheter is freshly placed under aseptic conditions).

Other Studies

As with laboratory data, ICU patients commonly undergo a considerable number of other diagnostic studies such as chest radiographs (CXRs) and computed tomography (CT) scans. As a rule of thumb, ICU providers should be aware of all study results of radiological studies performed or interpreted during the interval since the prior daily rounds and be prepared to discuss them on the current rounds.

The differential diagnosis in ICU patients for falling urine output and rising creatine, as well as fever/hypothermia and leukocytosis, and an annotated bibliography can be found at www.expertconsult.com.

Falling Urine Output and Rising Creatinine

With rare exception, a falling urine output (UOP) typically heralds the onset of acute renal failure (ARF) or, under more current terminology, acute kidney injury (AKI) (Chapter 81). AKI is a common occurrence in the ICU, with up to one third of patients experiencing some degree of AKI during an ICU admission. The drop in UOP is typically a result of decreases in the glomerular filtration rate (GFR) and is associated with the accumulation of urea, creatinine, and body fluids. The differential diagnosis for a rising creatinine and BUN in ICU patients is shown in Table 13.E1. These, in turn, result in various clinical abnormalities, e.g., changes in mental status, electrolyte abnormalities, derangements in acid-based balance, and volume overload. The presence of AKI can have a profound impact on ICU care and outcomes, resulting in prolonged ICU and hospital stays as well as a higher risk of death (~50% of ICU patients who develop AKI in the ICU die). Additionally, it can result in substantial increases in cost. However, renal failure is typically a reversible process, provided an underlying etiology can be determined.

The kidneys have three major functions: filtration of the blood to eliminate metabolic waste, solute and acid-base balance, and volume management. AKI can therefore result in a loss of the ability to regulate any of those responsibilities. AKI typically occurs over a period of hours to days and can occur de novo or in addition to underlying chronic renal dysfunction. Renal failure can be defined as *nonoliguric* (> 400 mL UOP/day), *oliguric* (< 400 mL UOP/day), and *anuric* (< 100 mL UOP/day). All three result in variable reductions in the ability to maintain the necessary renal functions.

There are three classifications of AKI: prerenal, intrarenal (intrinsic), and postrenal. Briefly, prerenal AKI results from renal hypoperfusion, intrinsic AKI results from parenchymal disease, and postrenal AKI results from urinary tract obstruction (Box 13.E1).

Prerenal AKI is the most common of the three and occurs because of a deficit in effective intravascular circulating volume. Therefore anything that reduces renal perfusion can precipitate prerenal AKI. Examples include hypotension, volume depletion (e.g., dehydration, hemorrhage, gastrointestinal losses, burns, renal losses, increased insensible loses), redistribution of volume (e.g., capillary leak syndromes, vasodilation, disorders of oncotic/hydrostatic pressure), cardiac dysfunction (e.g., congestive heart failure [CHF]), and medication effects on the renal vasculature (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme [ACE] inhibitors).

Intrinsic AKI results from disorders that affect the renal parenchyma, including the vasculature, glomerulus, interstitium, and tubules. The most common form of intrarenal AKI is acute tubular necrosis (ATN). ATN has multiple etiologies, including ischemia and exposure to nephrotoxic medications. Common nephrotoxic drugs encountered in the ICU include NSAIDs, aminoglycosides, angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers

TABLE 13.E1 ■ **Differential Diagnoses for Elevated Creatinine and Increased Blood Urea**

Elevated Serum Creatinine Level	Elevated Blood Urea Nitrogen-to-Creatinine Ratio (> 20:1)
Rhabdomyolysis	Excessive protein loading (e.g., > 1.5 g protein/kg/day)
Drugs that interfere with tubular secretion of creatinine (cimetidine and trimethoprim)	Increased catabolism (glucocorticosteroids, tetracyclines)
Drugs that interfere with laboratory assay for creatinine (serum ketones, cefoxitin)	Intravascular volume contraction with low urine flow states
Renal failure (acute kidney injury)	Gastrointestinal bleeding (with digested blood causing disproportionate rise in BUN)

BUN, blood urea nitrogen.

BOX 13.E1 ■ Differential Diagnosis for Acute Renal Failure/Acute Kidney Injury in the ICU

Prerenal

- Hypotension
- Volume depletion
  - Dehydration
  - Hemorrhage
  - Gastrointestinal losses
  - Burns
  - Renal losses
  - Insensible losses
- Redistribution of volume
  - Reduced oncotic pressure
  - Increased hydrostatic pressure
  - Capillary leak syndromes
  - Vasodilation
- Cardiac dysfunction
- Medication effects
- Other
  - Auto-PEEP
  - Intra-abdominal hypertension

Intrinsic Renal

- Tubular injury
  - Acute tubular necrosis (ischemia, toxin)
- Renal interstitial disease
  - Interstitial nephritis (infection, drugs)
- Glomerular injury
  - Glomerulonephritis (infection, autoimmune)
- Vascular dysfunction or injury

Postrenal

- Obstruction

Auto-PEEP, auto-positive end expiratory pressure

(ARBs), and radiocontrast agents (e.g., IV contrast dye). Additionally, it is important to note that persistent prerenal AKI can progress to ATN if not adequately treated.

Postrenal AKI results from obstruction of the urinary tract. Most commonly it is a consequence of obstruction at the level of the neck of the bladder (the communication between the bladder and urethra), either from intrinsic obstruction (e.g., urinary tract infection) or extrinsic compression (e.g., prostatic hypertrophy) in an uncatheterized patient. In a patient with a urinary catheter, it can result from obstruction of the catheter. Less commonly, postrenal AKI results from a more proximal site of obstruction at the level of the ureter. However, postrenal AKI in this case requires either bilateral ureteral obstruction or unilateral obstruction in a patient with a single kidney in order to result in renal failure.

The diagnostic approach to the patient with AKI (see Figure 13.E1) includes a careful assessment of the patient's history and physical exam, evaluation for obstruction, microscopic and other examination of a freshly voided urine sample, serologies, and other diagnostic tests. Important elements of the history and physical to address include an underlying history of renal disease, pertinent events in the preceding 24 hours, medication reconciliation for the presence of nephrotoxic agents, the presence or absence of a urinary catheter, and a review of the total intake and output

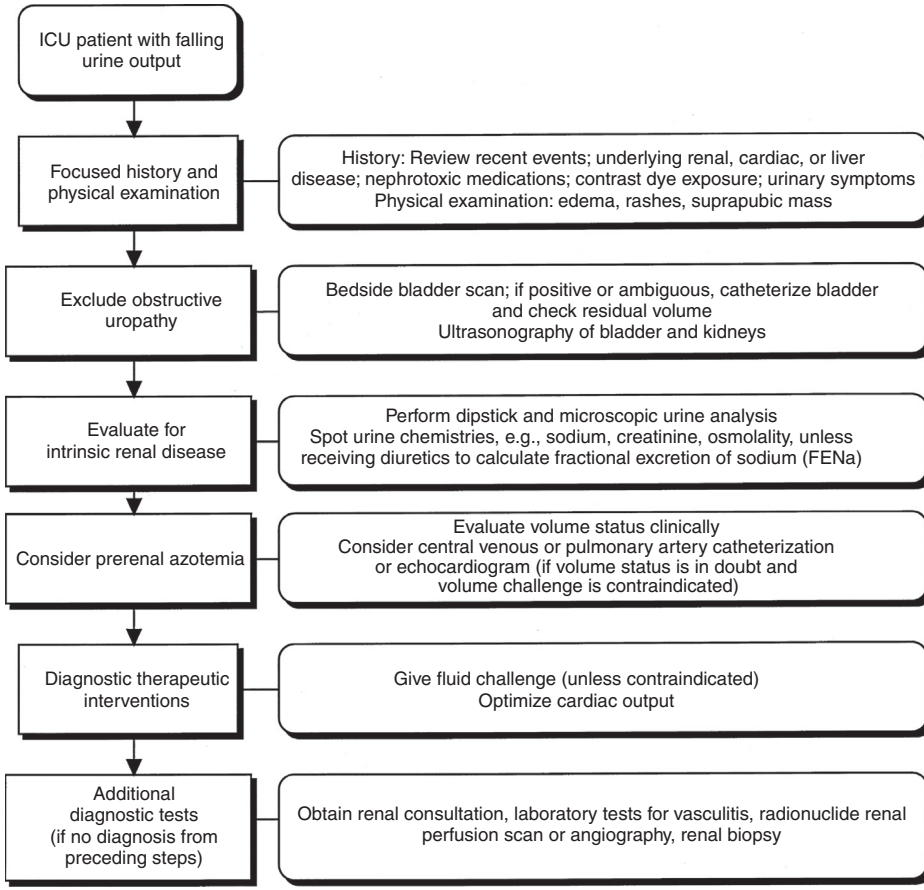


Figure 13.E1 Schematic flow diagram that illustrates the general diagnostic approach to the development of acute kidney injury in ICU patients.

throughout the hospital stay, in particular the previous 24 hours. Additionally, an assessment of hemodynamics, jugular venous pressure, skin turgor, presence and degree of soft tissue edema in extremities or other dependent locations and presence and degree of ascites can provide information about the etiologies of AKI.

Once the general evaluation is completed, the workup for AKI should first rule out obstruction as the etiology. In a noncatheterized patient, a urinary catheter should be placed to decompress an obstruction at the bladder neck. In a catheterized patient, the catheter can either be flushed or replaced. Alternatively, a bedside bladder scan can be obtained to look for retained urine. If there is no evidence for obstruction at this site, a renal ultrasound should be obtained to rule out ureteral obstruction. Lastly, a urinalysis can reveal a potential infectious etiology for obstruction. Abnormal findings suggestive of infection can include pyuria, hematuria, positive leukocyte esterase, or presence of urine nitrites.

If no obstruction is identified, assessment of urinalysis and urine electrolytes can help distinguish between prerenal and intrinsic AKI. In patients with prerenal AKI, the specific gravity tends to be higher (often > 1.020). Measurement of fractional excretion of sodium (FE_{Na}) is characteristically < 1% (where FE_{Na} = [urine Na × plasma Cr × 100] / [plasma Na × urine Cr]).

Conversely, urine specific gravity tends to be lower and FE_{Na} higher (> 1%) with intrinsic AKI. Other urinalysis findings consistent with intrinsic AKI are the presence of protein, which can suggest glomerular disease; blood, which can represent glomerular or tubular injury; and sterile pyuria with or without eosinophils, suggestive of acute interstitial nephritis (AIN). (See Chapter 81 for more details). An analogous fractional excretion of urea can be calculated when FENa would be inaccurate, such as after diuretic administration.

Other laboratory data may provide additional clues to systemic illness manifesting, in part, with AKI. Thrombocytopenia with hemolytic anemia can suggest a consumptive coagulopathy such as thrombotic thrombocytopenic purpura (TTP) or disseminated intravascular coagulation (DIC) (Chapter 45). Eosinophilia may aid in the diagnosis of AIN. Elevated creatinine kinase (CK) could suggest rhabdomyolysis (Chapter 81). In the appropriate clinical setting, electrolyte abnormalities could be consistent with tumor lysis syndrome. Lastly, specific serologic studies for collagen vascular disease could reveal evidence of vasculitis (e.g.,Wegener granulomatosis, Churg-Straus syndrome) or antiglomerular basement membrane disease (Goodpasture syndrome) with or without associated diffuse alveolar hemorrhage (Chapter 78).

When the etiology of the AKI remains unclear, additional invasive testing can be performed, including radionuclide scans to assess for vascular occlusion or a CT-IV pyelogram to further evaluate possible obstructive etiology. Renal biopsy is also a possible diagnostic test that can further clarify types of intrinsic AKI. When considering these tests, renal consultation is indicated.

One final test worth discussing further is the measurement of bladder hydrostatic pressures, which can be obtained via a transducer that attaches to the urinary catheter. Bladder pressures are surrogates for intra-abdominal pressure measurements and are useful to diagnose intra-abdominal hypertension (IAH) or abdominal compartment syndrome (ACS) as the source for impaired renal perfusion (Chapters 90 and 97). Patients in the ICU—particularly those receiving large-volume resuscitation for sepsis or surgical patients with intra-abdominal surgeries or trauma—are at high risk for developing IAH and ACS, which can impair blood flow to the kidneys and result in either prerenal AKI or ultimately intrinsic AKI (ATN). Assessments of bladder pressure can be used to rule out ACS as the source of AKI in this context. A normal bladder pressure is < 10 mm Hg, with AKI commonly occurring in the setting of bladder pressures > 20 mm Hg. (See Chapter 97.)

Management of all types of AKI (Table 13.E2) should be directed at optimizing volume status and renal perfusion, avoiding nephrotoxic drugs, correcting electrolyte and acid-base abnormalities, and treating the underlying etiology. The therapeutic interventions for postrenal AKI are directed to relief of the obstruction. Treatment of intrinsic AKI consists mainly of supportive care and reversal of the underlying disorder.

Treatment of patients with prerenal AKI is based on the etiology of the prerenal state. In prerenal AKI resulting from volume depletion or redistribution of volume away from the intravascular space, a volume challenge should be performed. Two types of fluids can be administered: crystalloid and colloid. In multiple randomized trials, use of colloid-containing solutions has not improved outcomes compared to crystalloids in terms of mortality or reversal of AKI in ICU patients (and may increase risk of AKI in some studies). However, one current exception to this practice of avoiding colloids for volume expansion is in the use of albumin products in cirrhotic patients with either spontaneous bacterial peritonitis (SBP) or undergoing large-volume paracentesis. In this one specific context, evidence suggests that albumin administration may result in better outcomes than infusing crystalloid as the resuscitating fluid.

When infusing a crystalloid, an isotonic solution should be selected. The type of isotonic solution is generally not critical and, although still subject to debate, sodium bicarbonate solutions may reduce risk of contrast nephropathy when compared to isotonic saline (0.9%). The appropriate volume and rate of a crystalloid infusion is not standardized, but generally boluses of 500 to 1000 mL (~15 mL/kg PBW) of isotonic crystalloid over 1 to 2 hours is a reasonable starting point. In prerenal AKI, the goal of resuscitation should be, at the very least, to match

TABLE 13.E2 ■ **General Approach to the Management of Acute Renal Failure/Acute Kidney Injury**

Management Steps	Description
1. Assess for recent changes in medical status	Events of last 24 hours, focused physical exam, review of exposure to nephrotoxic agents, assessment of intake and output
2. Rule out obstruction as the precipitating factor	Place or replace urinary catheter, bladder scan, renal ultrasound, urinalysis
3. Correct prerenal factors, maintain renal perfusion, and establish urine output	Fluid challenge, inotropic agents, diuretics
4. Address biochemical complications	Measure electrolytes at least daily; correct electrolyte and acid-base abnormalities
5. Prevent further renal injury	Avoid nephrotoxins; volume expansion diuresis for crystalluria, pigmenturia, significant trauma, major vascular surgery, radiocontrast agents, amphotericin B, cisplatin
6. Fluid and electrolyte management	Maintain euvolemia (e.g., match intake = prior day's output plus insensible losses), limit daily potassium and sodium intake, avoid magnesium-containing antacids, give phosphate binders enterally
7. Provide adequate nutrition	Minimize negative nitrogen balance
8. Monitor drug therapy	Adjust dosing; measure drug levels
9. Hemodialysis or ultrafiltration	Indicated for symptomatic uremia, fluid overload that is unresponsive to conservative measures, intractable hyperkalemia, acidemia, pericarditis or bleeding

total output in real time. In other words, it is important to pay attention to the patient's total output at least every 4 to 8 hours to avoid falling behind in matching intake and output. Of note, when volume depletion or redistribution of intravascular volume results in hypotension, vasoconstricting medications may be necessary in addition to IV fluids in order to generate sufficient systemic vascular resistance (SVR) to maintain mean arterial pressure (MAP) (usually at or above MAP of 60-65 mm Hg is regarded as sufficient) and thus renal perfusion pressure.

Alternatively to intravascular volume depleted states, when prerenal AKI results secondary to cardiac dysfunction (e.g., CHF), the intravascular volume is elevated. In this situation, it may be necessary to administer a diuretic, rather than a fluid challenge, to reduce cardiac work and improve renal perfusion. Afterload reducing agents and inotropic agents may need to be administered in conjunction with the diuretic to facilitate effective diuresis (Chapter 52).

When volume status is unclear, invasive monitoring may be needed to provide more insight into the circulating blood volume. A central venous catheter (CVC) can be placed to allow measurement of a central venous pressure (CVP) as well as central venous oxygen saturation (Scv_{O2}). Alternatively, a pulmonary artery catheter (PAC) can be placed to measure pulmonary arterial and occlusion pressures and mixed venous oxygen saturation (Sv_{O2}) (Chapters 7 and 11). Bedside ultrasound that measures percent collapse of inferior venal cava (IVC) during inspiration (which correlates with right atrial [RA] pressure) may also provide useful information on the volume status of the right side of the circulation: 100% IVC collapse correlates with a RA pressure of 0-5 mm Hg; > 50% collapse with RA of 6-14 mm HG; < 50% collapse with RA of 15-19 mm Hg and 0% collapse with RA pressure of 20 mm Hg or greater.

When management of AKI does not result in improvements in renal function and UOP, renal replacement therapy (RRT), e.g., dialysis, may be required to treat sequelae of renal failure. In the ICU, the most common consequences of persistent renal failure that result in a need for RRT include mental status changes or severe nausea and vomiting due to uremia, volume overload,

electrolyte imbalances, acid-base derangements, uremic pericarditis and a uremic bleeding diathesis. Any of these complications warrants consultation with the renal service for evaluation for RRT (Chapter 20).

Fever/Hypothermia and Leukocytosis

Fever (or hypothermia), leukocytosis, or both are common in the ICU and can have infectious and noninfectious etiologies (Tables 13.E3 and 13.E4). Because of the challenges ICU patients face (multiorgan failure, immunosuppression, indwelling lines and catheters, sedation, paralysis, etc.), it is reasonable to presume a rise in a patient's temperature curve or a rise in a patient's WBC count is in response to an infectious process. Since ICU patients are susceptible to infections in multiple locations, a thorough and systematic evaluation process is required.

Traditionally in hospitalized patients, fever is defined as a temperature exceeding 38° C (100.4° F) and hypothermia is defined as a temperature less than 35° C (95° F). However, because every patient has a unique temperature range, attention to trends in temperature can be more useful than isolated measurements. There are a number of methods for measuring temperature. In general, measurement of core body temperature is more accurate than axillary or skin temperature. Core temperature can be estimated by the oral, rectal, or tympanic membrane route. Rectal measurement is the most accurate representation of core body temperature. However, in the ICU population, rectal temperatures can be difficult to perform because of issues with patient mobility and are contra indicated in neutropenic patients. Likewise, oral temperatures can be challenging because of the presence of an endotracheal tube in the mouth. One additional source of temperature measurement unique to the ICU setting is bladder catheters with self-contained temperature probes, facilitating continuous measurement that can be displayed on the room monitor.

TABLE 13.E3 ■ **Infectious Causes of Fever in the Intensive Care Unit**

Abdominal, gastrointestinal	Acalculous cholecystitis; appendicitis; diverticulitis; intra-abdominal, pelvic, or retroperitoneal abscess; liver abscess; mesenteric infarction; peritonitis; pseudomembranous colitis; viral hepatitis (transfusion related)
Nosocomial infections	Intravascular catheter–related infection (phlebitis; cellulitis; bacteremia/fungemia; endocarditis, septic thrombophlebitis, or both), pneumonia, sinusitis, systemic candidiasis, tracheobronchitis, urinary tract infection
Surgical	Deep operative infection, infected prosthesis, retained surgical sponge, wound infection

TABLE 13.E4 ■ **Noninfectious Causes of Fever in the Intensive Care Unit**

Inflammatory	Allergic drug reaction, allograft rejection, aspiration pneumonitis, atelectasis, crystalline arthritis (gout, pseudogout), neoplasm, pancreatitis, postpericardiotomy syndrome, transfusion reaction, vasculitis
Metabolic	Alcohol and sedative withdrawal (Chapter 31), hypoadrenalism, malignant hyperthermia (Chapter 55), neuroleptic malignant syndrome (Chapter 55), serotonin syndrome (Chapter 57), thyrotoxicosis (Chapter 85)
Neurologic	Aseptic meningitis, dysautonomias, spinal cord injury (C4 and C5), subarachnoid hemorrhage, thermoregulatory disorders resulting from hypothalamic injury (e.g., after cardiac arrest [Chapter 49] or head trauma [Chapter 99])
Vascular	Aortic dissection, deep venous thrombosis, myocardial infarction, pulmonary embolism, hemorrhage

Acute infection can present with hypothermia or with a fever. Patients considered more likely to present in this way include the immunocompromised, the elderly, and patients with chronic hepatic or renal disease. A common noninfectious cause of hypothermia is large-volume IV resuscitation, most commonly seen with trauma, sepsis, burn, and gastrointestinal (GI) bleed patients. Unless the resuscitation fluid is warmed or passes through a fluid warming device on route to the patient, IV administration will lower body temperature. Additionally, GI bleed patients frequently undergo gastric lavage as part of the diagnostic evaluation, which can have an effect similar to IV resuscitation.

Body temperature is regulated by the hypothalamus. Fever occurs when cytokines such as interleukins, tumor necrosis factor, or interferon disrupt the natural set point. Cytokines can be released in response to both infectious and inflammatory conditions. Infections are the most common cause of fever in ICU patients. As such, diagnostic and therapeutic interventions should address infection first.

As with abnormal temperature, a rise in the WBC count (leukocytosis) can result from both infectious and noninfectious conditions. The infectious causes of fever/hypothermia and leukocytosis are similar and are discussed next. An increase in the percentage of neutrophils, in particular immature band forms, on differential blood cell count analysis suggests an infectious cause.

Similar to hypothermia, there are infectious and noninfectious conditions that can result in a reduction in WBC count (leukopenia) rather than an increase. Most commonly, this occurs in the setting of bone marrow suppression. Sepsis-induced bone marrow suppression is one classic example of this phenomenon, though it is far more common that a patient will present with leukocytosis rather than leukopenia. The most common noninfectious etiology of incident leukopenia in the ICU is medication side effect.

INFECTIOUS CAUSES OF FEVER

Intravascular Infections

The majority of nosocomial infections are bacterial and involve the urinary tract, surgical wounds, respiratory tract, or intravascular devices (Chapter 14). Intravascular infections are one of the most common preventable causes of fever/leukocytosis in the ICU. As noted previously, patients frequently have vascular access devices such as central venous, dialysis, and arterial catheters to enable real-time monitoring of hemodynamics and to administer life-sustaining therapies. However, vascular devices also provide a direct conduit from the skin to the intravascular space, which can result in bloodstream infections (BSIs). Additional intravascular sources of infection include septic deep venous thromboses (DVT) and endocarditis. BSI can frequently be diagnosed with serial blood cultures. BSIs are discussed in detail in Chapter 14.

Respiratory Tract Infections

Respiratory tract infections, including tracheobronchitis and pneumonia, are another common cause of fever and leukocytosis particularly in mechanically ventilated patients. As with intravascular devices, the presence of an endotracheal tube tends to allow oral or aspirated microorganisms to gain access to the respiratory tract. Additionally, an endotracheal tube often necessitates the use of sedation for patient comfort. An unintended consequence is impairment of swallowing and cough reflexes, increasing the potential for aspiration and lower respiratory tract infections. Some clinical findings that may suggest a respiratory tract infection in the setting of fever include tachypnea, hypoxia, increased tracheal secretions, greater dependence on mechanical ventilation, abnormal chest radiograph (CXR), and abnormal sputum culture.

Nosocomial respiratory tract infections can be challenging to diagnose. First, there are a variety of noninfectious pulmonary processes that can precipitate fever, including atelectasis and pulmonary embolism. Second, the airways of patients with endotracheal tubes are routinely colonized

with microorganisms, making cultures unreliable. However, demonstration of WBC and the absence or only a few epithelial cells in the sputum Gram stain can help differentiate infection from colonization. Third, radiographic abnormalities can be misleading and may not represent a true pneumonia. Nevertheless, CXR and sputum (or tracheal aspirate) culture should be routinely ordered to aid in the diagnosis. If these initial studies are unrevealing but respiratory tract infection remains high on the differential diagnosis, additional tests such as chest CT scan, bronchoscopy or catheter-directed bronchoalveolar lavage (BAL) should be considered.

Chest CT scanning is a superior imaging technique to routine CXR and can be used to diagnose both parenchymal and pleural disease. Additionally, chest CT with pulmonary embolism protocol, i.e., with the use of IV contrast, can rule out pulmonary embolism (PE). However, CT requires transportation of a potentially unstable patient to radiology, making CXR the preferred *initial* imaging study.

The pleural space is an additional site that can harbor microorganisms and result in fever. Ultrasound of the chest is a safe, non-invasive test that can be performed at the bedside to evaluate for pleural effusions. The presence of increased fluid in the pleural space, especially in the context of a respiratory tract infection, can suggest a parapneumonic effusion or even an empyema that may require further evaluation and possibly drainage.

If sputum cultures or tracheal aspirates are unhelpful and imaging suggests the presence of parenchymal lung disease, bronchoscopy can be performed at the bedside to obtain better samples for diagnostic evaluation (e.g., bronchoalveolar lavage [BAL]). The sensitivity of BAL for diagnosing ventilator-associated pneumonia (VAP) is relatively high (~75%) as long as it is done prior to starting new antimicrobial therapy. After the start of new antimicrobials, however, BAL's sensitivity is too low (< ~25%) to be useful in some ICU clinicians' judgment.

Genitourinary Infections

Urinary tract infections (UTIs) are another source of fever and leukocytosis. As with vascular devices and endotracheal tubes, nosocomial UTIs are commonly catheter associated. Patients with critical illness often have indwelling bladder catheters to facilitate continuous measurement of urine output. Once again, an unintended consequence of an indwelling catheter is an increased risk of infection. As with respiratory cultures, positive urine cultures can represent either infection or colonization resulting from the chronic presence of indwelling urinary catheters during hospitalization. The recommended diagnostic strategy for a catheterized patient with a suspected UTI is to send a urinalysis (U/A) first without a culture (Chapter 14). If the U/A demonstrates evidence of infection, the catheter should be changed and a repeat U/A sent prior to initiating antimicrobial therapy. A positive repeat U/A suggests infection rather than colonization, and a quantitative urine culture should be sent. Additionally, empiric antimicrobial therapy may be started while awaiting results of the culture.

Abdominal Infections

The abdomen is an important potential site of infection in critically ill patients, in particular surgical patients. There are a number of intra-abdominal sites where infection can occur, including the hepatobiliary tree, solid organs, intestine, and peritoneal space. Acute cholecystitis is the most common infection of the hepatobiliary tree. In the general population, most cases of cholecystitis are due to gallstones. However, in the postoperative ICU population, up to 50% of cases of acute cholecystitis are *acalculous* (without stones). Cholecystitis is diagnosed by ultrasound of the hepatobiliary tree. Diagnostic abnormalities include gallbladder wall tenderness during scanning (sonographic Murphy sign), gallbladder wall thickening, pericholecystic fluid, and distention of the gallbladder. In the absence of these findings being definitively diagnostic, a hepatobiliary iminodiacetic acid (HIDA) scan (a nuclear medicine study) is an additional test that can aid in diagnosis. HIDA scans (when done in conjunction with IV morphine sulfate administration to stimulate the sphincter of

Oddi) has a sensitivity of 95% and a specificity of 85% to diagnose acute cholecystitis compared to an ultrasound's sensitivity of 85% and specificity of 60%. However, performing the HIDA scan correctly requires transport of the patient out of the ICU for several hours.

Solid organ causes of infection include abscesses and pancreatitis. These conditions can usually be made with abdominal CT. However, IV and oral contrast are required for an optimal study, which can be challenging in patients with multiorgan dysfunction (e.g., acute or chronic renal failure or bowel obstruction/ileus).

Intestinal etiologies include bacterial infection, in particular infection by *Clostridium difficile* associated with alteration of the normal gastrointestinal flora resulting from antibiotic use. The majority of patients developing a *C. difficile* infection have fever, diarrhea, and leukocytosis (and typically *extreme* levels of leukocytosis). Other intestinal etiologies of infection include appendicitis, diverticulitis, and perforation of the intestine secondary to intestinal infection, infarction, or obstruction. Testing stool for toxins of *C. difficile* is highly sensitive for ruling out *C. difficile* if negative. Abdominal CT scan with IV and oral contrast is usually sufficient to diagnose the majority of nosocomial intestinal infections.

Other Infections

Central Nervous System and Head and Neck Infections. The most common head and neck infection in the ICU is sinusitis. Patients are placed at higher risk because of the placement of nasogastric or nasoenteral tubes used for enteral administration of medication and nutrition (Chapter 16). Sinusitis is diagnosed by CT scan of the sinuses. Although uncommon, sinusitis must be considered in patients with nasal tubes and fever who do not have another obvious source of infection.

Nosocomial central nervous system (CNS) infections such as meningitis are extremely rare. Thus, lumbar puncture (LP) to sample cerebral spinal fluid and CNS imaging are not recommended as part of the routine evaluation of fever in the ICU. However, attention to the physical exam can reveal situations where CT of the head or LP might be appropriate (e.g., focal neurologic or meningeal signs). Exceptions where an LP might be warranted are neurosurgical and head trauma patients, patients with infections that are known to involve the meninges, and situations where the evaluation of mental status is limited (e.g., as a result of opioids or sedation).

Musculoskeletal Infections. Infections involving the musculoskeletal system include soft tissue infections such as cellulites, fasciitis, or abscesses and bone infections such as osteomyelitis. Cellulitis can be diagnosed by physical exam and requires no further testing. Fasciitis is a surgical emergency and requires prompt evaluation, including surgical consultation and, if necessary, imaging (Chapter 66). Osteomyelitis is best evaluated by nuclear or magnetic resonance imaging and requires prolonged antibiotic therapy. Abdominal abscesses can best be discovered via CT scanning with IV and oral contrast and usually require percutaneous or surgical drainage.

Perhaps the most common soft tissue infection seen in the ICU patient population occurs in areas of skin breakdown caused by immobility. Despite concerted efforts at skin care (e.g., turning patients routinely, keeping skin dry, minimizing volume overload, cleaning patients regularly), skin breakdown and ulcer formation occur with regularity in the ICU population at high risk for such complications (Chapter 42). Once the skin barrier is compromised, microorganisms can enter the space and cause both local and systemic infection. It is now a standard of care that skin be evaluated at regular intervals to ensure early identification of areas of concern and escalating management of persistent or worsening pressure ulcers.

Postoperative Infections. There are a number of classic infectious and noninfectious causes of fever in the postoperative patient. The timing of fever may give clues to the diagnosis. Fevers in the first 24 hours of surgery are most commonly secondary to noninfectious causes. Fevers 48 to 72 hours

after surgery are more commonly due to bloodstream infections and venous thromboembolism. Wound infections and pneumonia usually occur after ~5 days. Intra-abdominal abscesses usually do not present until ~1 week after surgery. Urinary tract infections can occur at any time in the postoperative period.

Fungal Infections. Fungal infections are an increasing problem in the ICU. Critically ill patients are frequently immunocompromised, are treated with broad-spectrum antibiotics, may receive corticosteroids (which further suppress the immune system), have various indwelling catheters and tubes, may have variable glucose control, and occasionally require nutrition to be administered parenterally. These are all independent risk factors for fungal infection. The most common type of fungal infection is due to *Candida*. Sites of *Candidal* infection include the bloodstream (fungemia), solid organs (particularly spleen and liver), skin, and eyes (endophthalmitis). Additionally, *Candidal* fungemia can sometimes result in endocarditis, a potentially devastating complication of ICU hospitalization. Another less common fungus seen in the ICU is *Aspergillus*, typically occurring in patients with neutropenia secondary to malignancy or chemotherapy (Chapter 24).

NONINFECTIOUS CAUSES OF FEVER

Noninfectious illnesses are an important cause of nosocomial fever in the ICU. Many of these conditions are discussed in greater detail in other chapters. Drug reactions commonly occur and are often manifested by fevers and skin rashes (see Chapter 43). Patients with prolonged immobility or recent surgical intervention may develop fevers because of venous thromboembolic disease (see Chapter 77). Some procedures may have a side effect of low-grade fever within the first 24 hours (e.g., bronchoscopy). Some disease processes themselves result in fever. Examples include hemorrhage into any body compartment, strokes (see Chapter 71), myocardial infarction (Chapter 50), aortic dissection (see Chapter 51), malignancy, and allograft rejection in transplant patients.

Withdrawal from drugs such as alcohol can also be associated with fever. Additional symptoms in the context of alcohol withdrawal syndrome (AWS) include tremors, diaphoresis, nausea, vomiting, tachycardia, hypertension, and hallucinations (Chapter 31). Similarly, withdrawal from corticosteroids can precipitate adrenal insufficiency, which can present with fever and hypotension, resembling sepsis. Ultimately, although there are a variety of noninfectious etiologies for fever, infection must *always* be ruled out.

DIAGNOSTIC ALGORITHM

The diagnostic evaluation of fever and leukocytosis should be systematic and timely (Figure 13.E2). The initial step should be a review of the list of current medications for potential offending agents. A careful physical exam should be performed with particular attention to the skin (e.g., pressure ulcers, erythema, or induration), extremities (for asymmetry or tenderness), mental status, and vital signs. Sites of all indwelling lines and catheters should also be assessed.

Laboratory evaluation should include two sets of blood cultures, urinalysis, and sputum culture, if there has been a change in sputum production or respiratory status. Preferably, the blood cultures should be obtained by fresh needle stick from two different sites to increase the likelihood that a positive culture represents infection rather than contamination or line colonization. If the patient has a new onset of diarrhea or abdominal pain or a new onset of extreme leukocytosis, a stool sample should be sent to the lab to be examined for *C. difficile* toxin (Chapter 38).

Routine studies should include CXR and sampling of any fluid collections as appropriate (e.g., ascites). As described previously, a lumbar puncture (LP) should be performed only in special circumstances. Other tests that may provide further information if the initial evaluation is unrevealing have been discussed throughout this chapter.

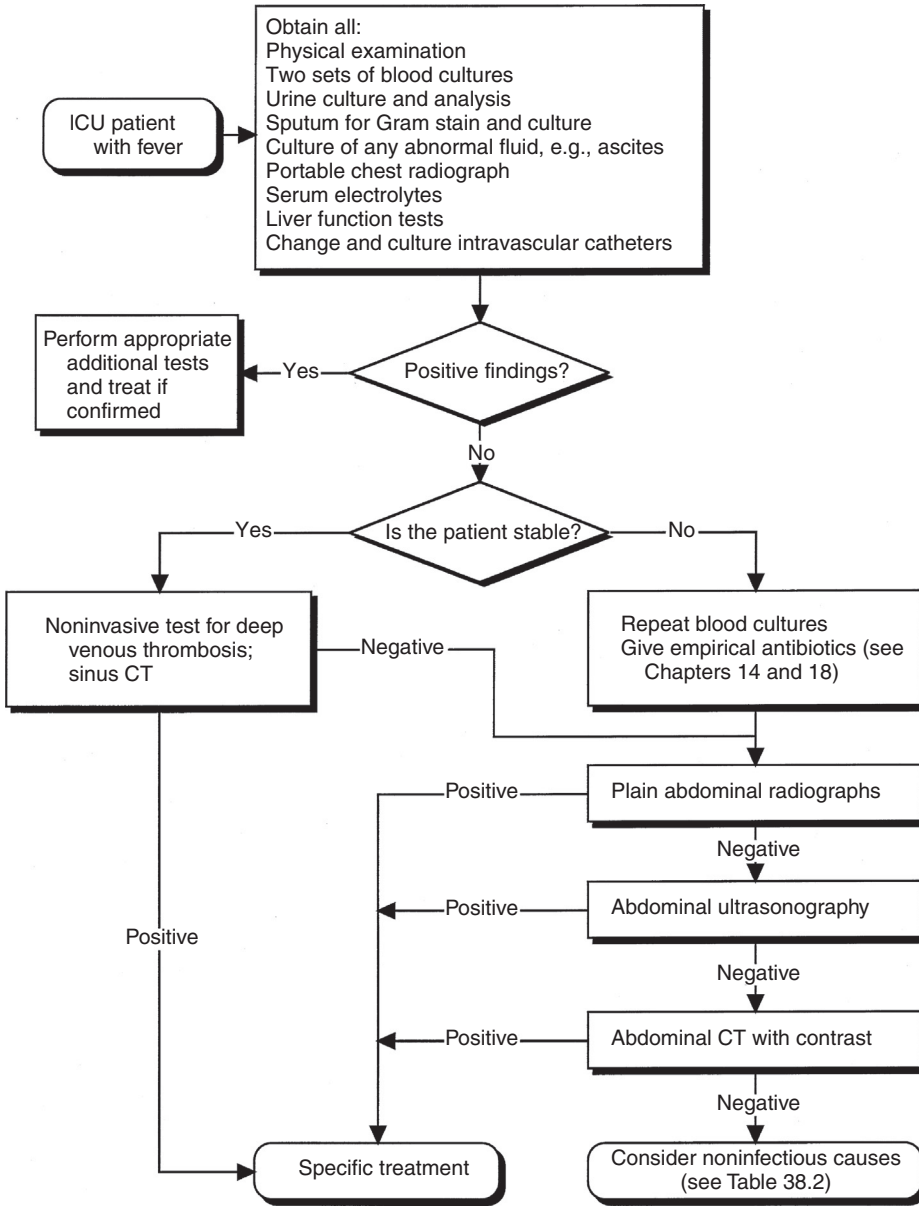


Figure 13.E2 Schematic flow diagram to evaluate fever in ICU patients.

MANAGEMENT

Management of fever and leukocytosis should first be directed at reversing the underlying process. Any offending medications should be stopped, if possible, to eliminate the possibility of drug fevers. Additionally, it is appropriate to remove any catheters or tubes that are no longer clinically indicated as soon as possible. Removal of vascular access devices in critically ill patients

can be difficult given their dependence on specific therapies that require central venous access and continuous hemodynamic monitoring. One option when fevers are suspected to be due to a BSI is to remove the catheter and observe a "line holiday" of up to 3 days prior to reinsertion. If this is not feasible, as is often the case, a new line is placed via a fresh needle stick. Alternatively, the catheter can remain in place, if the patient is stable, while waiting for the blood culture results.

The decision to treat fevers is somewhat controversial, as the fever itself may play a beneficial role in combating disease. However, it is generally accepted that for temperatures > 39° C (102° F), fever reduction is appropriate. The antipyretic of choice is generally acetaminophen. Aspirin and other nonsteroidal anti-inflammatory medications are less desirable because of the impairment of platelet function and risk of bleeding and renal dysfunction. Acetaminophen should be used with caution in patients with chronic liver disease or acute liver injury. In lieu of medication therapy, external cooling is another approach. However, it is less effective than antipyretic therapy.

Lastly, supportive care is an important part of the treatment of the febrile patient. Fever results in increases in metabolic rate, oxygen consumption, heart rate, respiratory rate, and insensible water loss. Administration of IV fluids and nutrition to combat insensible losses and support these increased demands is essential to maintain normal patient physiology and homeostasis in the ICU.

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CHAPTER 14

Health Care–Associated Infections

Joel Deitz ■ Keith Hamilton

The Centers for Disease Control and Prevention (CDC) estimates that 1 out of every 20 patients hospitalized in an acute-care hospital in the United States develops a health care–associated (nosocomial) infection (HAI), accounting for up to $45 billion in direct costs. HAIs occur 5 to 10 times more often in intensive care units (ICUs) and significantly increase morbidity, mortality, and length of hospital stay. This chapter describes the prevention, diagnosis, and treatment of the four most common HAIs in ICUs: (1) catheter-related bloodstream infections (CRBSIs), (2) ventilator-associated pneumonias (VAPs), (3) catheter-associated urinary tract infections (CAUTIs), and (4) surgical site infections (SSIs). Table 14.1 lists commonly associated organisms with these infections.

The risk of acquiring an HAI is influenced by numerous factors, including the patient's underlying disease; severity of illness; type of ICU; length of stay in the ICU; and number, type, and duration of invasive devices and procedures. Horizontal transmission of infections from patient to patient via ICU personnel or shared equipment is not uncommon, making the ICU setting particularly prone to clusters and outbreaks of infections.

Approach to Infection Control in the Intensive Care Unit

INFECTION CONTROL POLICIES

Preventable HAIs have become a national focus driven by advocates for patient safety, accreditation bodies, governmental agencies, insurance payers, and professional organizations. Effective prevention of HAIs requires a coordinated effort among infection control practitioners, the hospital epidemiologist, infectious diseases experts, microbiologists, and the ICU staff. All members of the ICU staff should become familiar with the hospital's infection prevention and control policies to prevent, diagnose, and treat HAIs. These policies typically include contact isolation precautions for patients infected or colonized with certain antimicrobial-resistant organisms including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and multidrug resistant gram-negative organisms in addition to patients infected with *Clostridium difficile*. Policies generally establish and standardize indications and basic practices for insertion, maintenance, monitoring, and discontinuation of catheters and other indwelling devices. Each institution should also standardize procedures for surgical antisepsis, instrument processing and sterilization, and timing and choice of perioperative antibiotic prophylaxis.

Policy development should be supplemented by HAI surveillance and direct observation of hand hygiene and other infection prevention practices. To be successful, infection prevention and control require a multidisciplinary collaboration to design and implement interventions in the ICU to decrease HAI rates.

The department of infection prevention and control should provide quantitative infection data to the ICU leadership team and staff so that HAIs can be investigated and appropriate prevention and quality improvement measures initiated.

TABLE 14.1 ■ **Sites of Intensive Care Unit Nosocomial Infections and Commonly Associated Pathogens**

Catheter-Related Bloodstream	Early-Onset Pneumonia (< 4 Days of Hospitalization) "Core Pathogens"	Late-Onset Pneumonia (≥ 4 Days of Hospitalization) "Core Pathogens"	Urinary Tract	Surgical Site
Coagulase-negative staphylococci	*Streptococcus pneumoniae*	*Pseudomonas aeruginosa*	Enterobacteriaceae*	*Enterococcus* spp.
Staphylococcus aureus	*Haemophilus influenzae*	Methicillin-resistant *Staphylococcus aureus*	*Enterococcus* spp.	Coagulase-negative staphylococci
Enterococcus spp.	Methicillin-sensitive *Staphylococcus aureus*	*Acinetobacter* spp.	*Pseudomonas aeruginosa*	*S. aureus*
Candida albicans	*Klebsiella pneumoniae*	Resistant enteric gram-negative bacilli	*Candida* spp.	*Pseudomonas aeruginosa*
Enterobacteriaceae*	Other nonresistant enteric gram-negative bacilli	"Core pathogens" seen in column to left	Other enteric gram-negative bacilli	*Enterobacter* spp.

*Enterobacteriaceae includes more than 70 genera of gram-negative bacilli, with *Escherichia coli, Klebsiella* species, and Enterobacter species most common in healthcare-associated infections.
Note: Late-onset pneumonias are commonly polymicrobial; early onset = less than 4 days in the ICU; late onset = 4 days or longer. See text for risk factors.

SPECIAL INFECTION RISKS IN THE INTENSIVE CARE UNIT

Rates of HAIs are generally higher in ICUs because of higher utilization rates of indwelling devices and because of the severity of illness and complexity of ICU patients. The ongoing need for all indwelling devices should be assessed daily. Devices should be removed immediately when their presence is no longer indicated or in cases when the device is suspected to be the source of infection, such as in the case of a CRBSI or CAUTI.

Broad-spectrum empiric antibiotic use is also more common in ICUs (Chapter 18), predisposing patients to infection or superinfection with fungal organisms, multidrug-resistant organisms (MDROs), and *Clostridium difficile*. To minimize these risks, the need for antibiotics should be carefully evaluated prior to their initiation. If antibiotics are necessary, the narrowest effective antibiotic regimen should be selected based on most likely organisms. However, before initiating empirical antimicrobial therapy, all appropriate cultures based on suspected sources of infection should be obtained so that the antibiotic regimen can be tailored to the cultures and susceptibility results. The continuation of empiric antimicrobial therapy is an issue that should be addressed daily on rounds and should be justified by culture results and the patient's clinical status (Chapter 18). Judicious antibiotic use should be viewed as a requisite for effective infection prevention and control.

Infections Due to Intravascular Catheters

CLINICAL DEFINITIONS AND SURVEILLANCE DEFINITIONS

A CRBSI is an infection of an intravascular catheter or catheter site with associated bacteremia. As with other device-associated infections in the ICU, it is important to understand the difference

BOX 14.1 ■ Risk Factors for Central Venous Catheter–Associated Infection

Concomitant total parenteral nutrition
Duration of catheterization*
Exposure to bacteremia or distant site of infection
Insertion with less than full barrier precautions or with poor skin preparation
Repeated catheterization
Site of insertion* (femoral > internal jugular > subclavian)
Type of catheter (triple lumen > single lumen; antimicrobial nonimpregnated > impregnated)

**Noted in some but not all studies.*

between *clinical* definitions (those used by clinicians to make a diagnosis and guide management) and *surveillance* definitions (those used by infection prevention and control personnel to monitor and report HAIs). Each definition has different objectives and has different criteria designed to achieve these goals. Therefore, a particular case may meet the surveillance definition but may not meet the clinical definition or vice versa.

The Infectious Disease Society of America (IDSA) has published clinical definitions and management recommendations for CRBSI (see "Diagnosis" and "Management and Treatment"). The CDC's National Healthcare Safety Network (NHSN) has developed the most widely used surveillance definitions. Unlike the IDSA definitions, the NHSN definition focuses only on infections caused by certain catheters (defined as central lines) and uses the term *central line–associated bloodstream infection* (CLABSI) to describe these infections. Central lines are catheters that terminate near the heart or in central blood vessels including aorta, pulmonary artery, superior vena cava, inferior vena cava, internal jugular, brachiocephalic, external iliac, common iliac, femoral, and, in neonates, umbilical vessels. Notably excluded from the CLABSI definition are extracorporeal membrane oxygenators (ECMOs), intraaortic balloon pumps (IABPs), femoral arterial catheters, and peripheral and midline intravenous (IV) catheters. On the other hand, the CRBSI definition includes *all* catheters. For the purpose of surveillance, CLABSI is defined by the presence of a catheter in one of the previously listed central blood vessels within 48 hours preceding the positive blood culture and the absence of another source to which the bacteremia can be attributed. For the diagnosis of CLABSI involving organisms that are commonly skin contaminants (e.g., coagulase-negative *Staphylococcus*), there must be two or more positive blood cultures plus systemic evidence of infection that cannot be attributed to another source.

INCIDENCE RATES AND PATHOGENS

The overall incidence of CLABSIs reported by NHSN is between 1.3 and 5.6/1000 catheter days (1 catheter day = 1 catheter in 1 patient for 1 day). Estimates are that the number of CLABSIs originating in ICUs has decreased by 58% from 2001 to 2009 at least in part because of an increased national focus on infection prevention and control. However, certain characteristics of ICU patients place them at higher risk (Box 14.1). Most CRBSIs are secondary to gram-positive organisms (see Table 14.1). Factors that increase the likelihood of gram-negative CRBSI include critical illness, neutropenia, prior antibiotic exposure, and femoral site. Factors that increase the likelihood of *Candida* CRBSI include parenteral nutrition, prolonged exposure to broad-spectrum antibiotics, hematologic malignancy, organ or bone marrow transplantation, femoral site, and presence of multiple sites of *Candida* colonization elsewhere in the patient (urine, respiratory, etc.).

As with other infections in the ICU, antibiotic resistance is a problem. Methicillin-resistant *S. aureus* (MRSA) represents over 50% of isolates of *S. aureus* in some regions. Vancomycin-resistant

Enterococcus (VRE) is also becoming a more prevalent cause of CRBSI. Emergence of extended-spectrum beta-lactamases (ESBLs) and carbapenemases in gram-negative organisms has resulted in resistance to most available antibiotics. There is increasing resistance to fluconazole among non-*albicans Candida* species, and fluconazole resistance has also been reported in *C. albicans*.

PATHOGENESIS

Short-term catheters are most commonly contaminated by skin flora entering at the insertion site and migrating along the outside of the catheter. Contamination of catheter hubs or lumens by contact with hands, access devices, or contaminated fluids can also occur. Hematogenous spread of bacteria from other sites is a less common cause of CRBSI. Interactions between the catheter and infecting organisms facilitate adhesion to the catheter and production of a biofilm, which helps certain infecting organisms to evade host defenses.

DIAGNOSIS

Except in cases when local inflammation is present around the catheter, the only signs of CRBSI are often fever or leukocytosis. Two sets of blood cultures should be obtained when signs and symptoms of infection are present, and positive blood cultures in the absence of another potential site of infection should raise the question of CRBSI. Blood cultures should be drawn before initiation of antimicrobial therapy, if possible, and from two peripheral sites (or one peripheral and one at the time of placing a new central line aseptically). If one sample is drawn from an existing central venous catheter, at least one other set should be obtained from a peripheral vein. If quantitative blood cultures are available, comparison of cultures drawn through the lumen of the suspected catheter to cultures from a peripheral site may aid in diagnosis. The threshold for diagnosis of CRBSI using this method is threefold or greater colony-forming units (CFU) in the blood culture drawn from the catheter compared to the blood culture drawn from another site. Automated blood culture systems, which continuously monitor growth and time to positivity, are commonly available. These systems allow for calculation of the difference in time between when peripheral cultures and when catheter cultures become positive, or differential time to positivity (DTP). The threshold for diagnosis of CRBSI by this method is positivity of the blood culture drawn through the catheter at least 120 minutes before the blood culture drawn from the other site.

If the catheter is removed due to suspected CRBSI, the catheter tip may be cultured as well. Appropriate catheter cultures include semiquantitative and quantitative catheter cultures. Semi-quantitative cultures are performed in the laboratory by rolling 5 cm of the catheter tip on a culture plate. The threshold for diagnosis of CRBSI by this method is > 15 CFU. Quantitative cultures are obtained by sonication and vortexing of the tip of the catheter to dislodge surface and intraluminal material into the culture medium. The threshold for diagnosis of CRBSI by this method is > 10^2 CFU. A positive culture of the catheter tip or of blood drawn through a catheter alone does not define a CRBSI. The diagnosis of CRBSI requires that signs of systemic infection are present and that blood cultures drawn from another site are positive with the same organism.

Meticulous aseptic technique is required when collecting all specimens. Skin and catheter access points must be prepped with 2% chlorhexidine (CHD), not povidone-iodine. Blood cultures should have the same volume of blood in all specimens in order to compare time to positivity or quantity of organisms.

PREVENTION

Efforts at prevention of CLABSI have yielded impressive and sustained results, including reports from many ICUs of no CLABSIs for extended periods of time. One simple yet effective means of

BOX 14.2 ■ Institute for Healthcare Improvement Central Line Bundle

Materials needed for CVC insertion available on a single cart or in a kit
Hand hygiene even when sterile gloves are used
Chlorhexidine (CHD) 2% used for skin antisepsis and allowed to dry
Full barrier precautions (mask, cap, sterile gown, sterile gloves, large sterile drape)
Avoidance of femoral site for placement

CVC, central venous catheter.
www.ihi.org/knowledge/Pages/Changes/ImplementtheCentralLineBundle.aspx.

preventing CRBSI is becoming familiar with appropriate indications for central venous catheters, placing those catheters only when appropriate indications are present, and removing catheters when those indications are no longer present. Steps should also be taken to prevent contamination at the time of insertion, which are often implemented in the form of a bundle, such as that advocated by the Institute for Healthcare Improvement (IHI) (Box 14.2). Emergently placed central lines (i.e., not placed using these techniques) should be removed within 48 hours. Catheter exchanges over a guide wire are discouraged except in rare cases because of high infection rates. A chlorhexidine (CHD)-impregnated sponge applied at the time of placement can further decrease infection rates.

Other successful interventions include the establishment of a culture of safety in the ICU, development of checklists to help achieve full compliance with prevention techniques, teaching and monitoring of competencies, feedback to practitioners of the data collected regarding outcomes, and support from administration to resource these efforts.

Hubs, needleless connectors, and injection ports should be disinfected before accessing the catheter. Transparent dressings should be used to cover the catheter exit site and should be changed every 5 to 7 days. Wet or soiled dressings should be replaced promptly. The catheter site should be inspected daily and the catheter removed if there are signs of inflammation. The continuing need for the catheter should also be reviewed daily and unnecessary catheters should be removed promptly.

If CLABSI rates remain high despite these interventions, other strategies can be used, including daily CHD bathing of high-risk patients and antibiotic or antiseptic-impregnated catheters and caps.

Intravenous (IV) administration sets should be changed daily if blood products or fat emulsions are given and changed every 6 to 12 hours if propofol is infused. Otherwise IV administration sets should be changed every 72 to 96 hours. Needleless systems should not include positive pressure mechanical valves. Properly placed and maintained CVCs do not need to be routinely replaced at regular intervals.

Although there are few data showing the development of resistant organisms when antibiotic-coated devices are used, there is still concern about antibiotic resistance arising over longer periods of time with widespread usage.

Another preventative technique is antibiotic-lock therapy (ALT), which consists of allowing high concentration of an antibiotic or other antimicrobial agent to reside inside the catheter in between usage. Some studies have shown benefit in preventing CRBSIs in patients with long term indwelling catheters, such as dialysis catheters, with the use of particular regimens. Further study of ALT to prevent CLABSI needs to be performed before this practice can be recommended.

Hemodialysis (HD) catheters are associated with higher infection rates than dialysis access by fistula or graft. If an HD catheter is needed for more than 3 weeks, infection rates can be decreased by the use of a tunneled catheter.

Arterial lines in adults should be placed in the radial, brachial, or dorsalis pedis artery rather than femoral or axillary artery. A minimum of sterile gloves, mask, cap, and a small fenestrated

drape are adequate precautions during insertion, except for femoral or axillary locations for which full barrier precautions are required. Transducers and other components of the system (other than the catheter) should be replaced at 96-hour intervals. Disposable transducers are preferred over reusable transducers for infection prevention. Dextrose containing flush solutions should be avoided. A closed flush system should be used, and strict aseptic technique should be maintained when accessing the system.

MANAGEMENT AND TREATMENT

The catheter should be removed if there are local signs of infection or inflammation. If the patient has hypotension, hypoperfusion, or organ failure, and there is no other obvious source of sepsis, the catheter should also be removed immediately. In some patients (e.g., clinically stable with difficult or dangerous to access blood vessels and without a clearly infected catheter), it may be reasonable to manage the patient without immediate catheter removal. In such cases, it may be reasonable to obtain blood culture through the catheter and a peripheral site and to remove the catheter if the DTP is > 120 minutes or if the patient does not improve. After appropriate cultures have been obtained, empiric antibiotics should be started and should include coverage for methicillin-resistant *S. aureus* (MRSA) and gram-negative rods (GNRs). The choice of antibiotic coverage for GNRs should be based on local antibiotic susceptibility patterns and prior cultures from the patient (Chapter 18). Antipseudomonal coverage should be initiated in all patients with neutropenia, severe illness, or known colonization with *Pseudomonas*. Antifungal coverage for *Candida* species should be considered in patients on parenteral nutrition, prolonged broad-spectrum antibiotics, hematologic malignancy, organ or bone marrow transplant, or multisite *Candida* colonization.

In general, once the diagnosis of CRBSI is established, the catheter should be removed if not done already. If the patient is clinically stable, it may be reasonable to attempt to sterilize an infected catheter without removing it under certain circumstances. If the patient has limited options for IV access and depends on long-term IV access for survival, removing the catheter may offer more risks than benefits. However, if the patient has impaired immunity, exit site or tunnel infection, presence of other intravascular hardware (e.g., mechanical heart valve), or infectious complications such as endocarditis, septic emboli, osteomyelitis, or suppurative thrombophlebitis, cure is unlikely and the catheter should be removed or changed. For short-term catheters, salvage should be attempted only for uncomplicated infections with coagulase-negative *Staphylococcus* (other than *S. lugdunensis*) and *Enterococcus* species; however, it should be acknowledged that treatment failure is more likely than if the catheter were removed. If salvage is attempted, the catheter should be removed immediately if there is no clinical improvement or if blood cultures remain positive after 72 hours of appropriate antibiotic therapy. If catheter salvage is attempted, systemic antibiotics may be supplemented by intraluminal antibiotic lock therapy or continuous infusion. Success at eradicating a CRBSI without catheter removal is uncommon with *S. aureus*, *Pseudomonas*, fungi, and mycobacteria.

Ventilator-Associated Pneumonia

DEFINITIONS

Ventilator-associated pneumonia (VAP) refers to pneumonia that is newly acquired during endotracheal intubation or with a tracheostomy. VAP is not intended to include pneumonias that are acquired prior to intubation and progress to require mechanical ventilatory support. Generally, VAPs arise at least 48 hours after endotracheal intubation. However, the NHSN surveillance definition of VAP includes any pneumonia arising in a tracheally intubated patient regardless of how soon it arises after intubation and pneumonias that arise within 48 hours

after extubation. Ventilator-associated tracheobronchitis (VAT) is defined as a lower respiratory infection that arises during tracheal intubation without radiographic evidence of pneumonia. The NHSN has proposed broader surveillance reporting of adverse events during mechanical ventilation, including ventilator-associated event (VAE), ventilator-associated condition (VAC), infection-related ventilator-associated condition (IVAC), possible pneumonia, and probable pneumonia.

VAP is a subcategory of hospital-acquired pneumonia (HAP), which is a pneumonia that is acquired in the hospital and is diagnosed at least 48 hours after admission. HAP is a subcategory of health care–associated pneumonia (HCAP), which is a pneumonia that develops in a patient with certain types of recent medical care. The importance of distinguishing these categories of pneumonia from community-acquired pneumonia (CAP) (Chapter 65) is that these infections are likely to be associated with pathogens that are more antibiotic resistant. Although the concept of VAP is relatively straightforward, there is no agreement on standards for clinical diagnosis (see "Diagnosis").

The term *ventilator-associated respiratory infection* (VARI) includes both types of ventilators associated lower respiratory tract infections, VAP and VAT. HAP is a subcategory of health care-associated pneumonia (HCAP), which is defined in the ATS/IDSA guidelines (2005) as a pneumonia that occurs in a "patient who was hospitalized in an acute care hospital for 2 or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic (within the past 30 days of the current infection)."

RATES AND RISK FACTORS

NHSN data indicate that the incidence of VAP has been decreasing, perhaps related to infection control measures. The mean/median rates of VAP vary from 0/0 per 1000 ventilator days for respiratory care units to 6.0/5.3 per 1000 ventilator days for trauma units. Nonetheless, VAP had been estimated to occur in up to 27% of ventilated patients with an attributable mortality of 9%.

Risk factors for VAP include potentially modifiable factors such as duration of intubation, impaired consciousness, immune suppression, low pressure in the endotracheal tube cuff, nasal intubation, lack of head elevation, transport out of the ICU, red blood cell transfusion, observed aspiration, and a low staff-to-patient ratio (Box 14.3). Nonmodifiable factors, such as extremes of age, prior antibiotic treatment, and underlying lung disease, are also risk factors for VAP. Suppression of gastric acid, although helpful to decrease stress-related upper gastrointestinal

BOX 14.3 ■ Risk Factors for Ventilator-Associated Pneumonia

Age ≥ 60 years
Chronic pulmonary disease
Coma, impaired consciousness, intracranial pressure monitor
H_2 histamine receptor blocker use, gastric colonization, and elevated gastric pH
Large-volume gastric aspiration
Mechanical ventilation ≥ 2 days
Organ failure
Reintubation
Supine head position

Adapted from Craven DE, Steger KA: Epidemiology of nosocomial pneumonia: new perspectives on an old disease. Chest 108:1S-16S, 1995.

bleeding, has been variably associated with risk of VAP, and the preferential use of H_2-histamine receptor blockers over proton pump inhibitors in ventilated patients is an unresolved issue.

PATHOGENESIS

The pathogenesis of VAP most commonly involves the colonization of the upper aerodigestive tract with pathogenic organisms and the subsequent entry of these organisms to the lower respiratory tract in large enough numbers to overcome host defenses, thus establishing an infection. Critically ill patients, especially those patients with a disease- or treatment-induced immune impairment or with prior antibiotic exposure, typically have an alteration in microbiologic flora in their aerodigestive tract to more pathogenic organisms. These organisms most commonly gain access to the lower respiratory tract (LRT) when secretions leak into the upper trachea through the epiglottis, which is held open by the endotracheal tube (ETT) and through the incomplete seal created by the vocal cords around the ETT. These organisms gain access to more distal airways by passing around the ETT cuff or through channels formed in the folds of the ETT cuff. Mechanical LRT defenses, such as mucociliary clearance and cough, are impaired by the ETT and by medications. Another route by which pathogens gain access to the LRT is via the ETT lumen often by colonization of the ETT and the biofilm that develops there. More rarely, aerosolization or aspiration of contaminated material via respiratory equipment or medication has been reported to be a cause of VAP. Hematogenous seeding of the lung and direct extension from an adjacent focus of infection are less common pathogenic mechanisms for VAP.

DIAGNOSIS

The clinical diagnosis of VAP is generally made when an endotracheally intubated patient develops a new infiltrate associated with signs of infection, including fever, leukocytosis, and purulent respiratory secretions. Making the diagnosis of VAP can be difficult in some situations. Radiographic infiltrates are not specific for pneumonia and can be caused by many processes other than pneumonia, such as atelectasis or pulmonary edema. Conversely, portable chest radiographs are not sensitive for detecting new infiltrates, especially in the presence of prior lung disease. Chest computed tomography (CT) may be more sensitive, but concerns about increased radiation exposure and safety issues related to transporting critically ill patients limit its use.

The gross appearance of sputum may suggest infection, but it is not specific because many patients have purulent secretions in their proximal airways as a result of colonization, irritation, and localized infection in the absence of pneumonia. A negative sputum culture obtained in the absence of antibiotics is considered adequate to rule out many types of bacterial pneumonia. A number of methods of quantitative and semiquantitative sputum culture, obtained either invasively (bronchoscopically) or non-invasively, have been advocated as criteria for VAP. The sensitivity of culture methods decreases if a new antibiotic has been introduced prior to obtaining the specimen. Most important, the absence of a gold standard for the diagnosis of VAP has hampered the ability to create a consensus regarding the use of these methods. Although some studies using quantitative cultures have shown decreased use of antibiotics without adverse clinical effect on patient outcomes, it has been difficult to show improvement in patient outcomes. It is important to remember that nosocomial pneumonia is caused by certain bacteria (e.g., *Legionella*) and many nonbacterial organisms that may not be detected by routine sputum bacterial cultures.

The Clinical Pulmonary Infection Score (CPIS), including modifications, has been advocated to improve VAP diagnosis. CPIS is the sum of values (0 to 2) assigned to five parameters (sputum, infiltrate, leukocyte count, fever, Pao_2:FIo_2 ratio) with a value less than 6 indicating that a pneumonia is not likely to be present. Concerns about the reproducibility of this score among various observers and the lack of consistent benefit from the clinical use of CPIS in studies have lead to limited adoption.

TABLE 14.2 ■ **Proposed Thresholds to Diagnose VAP**

Technique	Positive Threshold
Protected specimen brush	≥ 10^3 CFU/mL
Bronchoalveolar lavage (including mini BAL, with or without balloon-tipped catheter, with or without bronchoscopy)	≥ 10^4 CFU/mL
Tracheal aspirate	≥ 10^5 (to 10^6) CFU/mL

CFU, colony forming unit.

Inflammatory markers in serum and sputum have been investigated to improve VAP diagnosis and therapy. Procalcitonin (PCT) tends to rapidly rise with bacterial, but not viral, infections and fall rapidly with the resolution of the infection. Although PCT has shown promise as an indicator of when it is safe to stop antibiotics, it has not been sensitive enough to rule out VAP in a timely manner. Therefore antibiotics should not be withheld because of a low PCT result in a patient with suspected VAP. Other markers, such as C reactive protein (CRP), soluble trigger receptor on myeloid cells-1 (sTREM-1), and fibrin fibers in bronchoalveolar lavage (BAL) have not shown consistent utility in the diagnosis of VAP (see Table 14.2).

PREVENTION

VAP prevention efforts can be categorized into three areas: (1) decreasing the amount of time the patient is at risk for VAP, (2) preventing the proliferation of pathogenic microorganisms in the upper respiratory and digestive tracts, and (3) preventing access to the lower respiratory tract by these pathogenic microorganisms. Similar to the decreases seen in CLABSIs with the introduction of infection prevention measures in the format of a bundle, VAP rates have also decreased when such measures are implemented. Many of these bundles incorporate at least one strategy from each of the three categories. To be effective, these efforts must be coupled with broader efforts to decrease nosocomial infections, such as hand hygiene, isolation practices, adequate staffing, and limiting red blood cell transfusions.

Decreasing the time at risk for VAP can be accomplished by avoiding endotracheal intubation and by extubation as soon as the patient is able to sustain respiration independent of mechanical ventilation. In appropriate patients, such as those with exacerbation of chronic obstructive pulmonary disease (COPD) or decompensated congestive heart failure (CHF), non-invasive ventilation (Chapter 3) may offer the patient an alternative to intubation. Impairment of mentation by medication can delay extubation. Minimizing sedation, such as by daily sedation interruption, especially when coupled to daily assessment of the ability of the patient to be liberated from mechanical ventilation, appears to decrease the duration of mechanical ventilation and the incidence of VAP (Chapter 5). Weaning protocols also have been shown to shorten the duration of mechanical ventilation and improve outcomes (Chapter 4).

The most commonly employed practices to decrease proliferation of pathogenic microorganisms in the upper aerodigestive tract are oral care with antiseptics and oral, as opposed to nasal, intubation of the trachea and stomach. Nasal intubation can lead to obstruction of normal sinus drainage, leading to accumulation of secretions and subsequent proliferation of pathogenic microorganisms in sinuses, which then enter the LRT. Oral care with CHD has been associated with a lower VAP rate. In general, oral care should be performed several times a day, but the optimal frequency has not been determined.

Selective decontamination of the digestive tract (SDD) involves the administration of antibiotics or antiseptics applied in the mouth and stomach with or without concomitant systemic antibiotics. SDD has been successful in decreasing the incidence of VAP with minimal short-term impact on

antimicrobial resistance. However, concern about induction of resistance over longer periods of time and about scant evidence for improved mortality has limited adoption of this practice.

Endotracheal tubes (ETTs) impregnated with antiseptics such as silver or with other compounds designed to decrease biofilm have been employed. Studies of these ETTs have shown a decrease in colonization and microbiologically confirmed VAP, but other clinical outcomes, such as length of stay and mortality, were not improved. Probiotics, or microorganisms administered to the patient for therapeutic purposes, may prevent or replace colonization of the airways by pathogenic organisms. Studies of probiotics with various protocols have had varying results. More study is necessary before any of these measures can be recommended for routine use.

The most commonly employed measure to prevent aspiration in intubated patients is elevation of the head of the bed (HOB) to between 30 and 45 degrees. This practice, along with prevention of gastric overdistention, is designed to prevent reflux of gastric contents into the upper airway. Most ventilator bundles employ elevation of HOB and have been successful in reducing VAP incidence. Unless a contraindication to elevated HOB is present, the supine position should be avoided in ventilated patients.

Selective subglottic suctioning (SSS) utilizes a specialized ETT with a proximal suction port that drains the secretions that have entered the trachea above the ETT cuff. Reductions in VAP incidence, especially in patients who are intubated for longer than 72 hours, have been seen with SSS, but studies have not demonstrated mortality benefit. Problems with suction port occlusion have led to the use of intermittent suction and to tubes with multiple ports for SSS. Low ETT cuff pressures (below 20 cm H_2O) have been associated with an increased incidence of VAP, whereas ETT cuff pressures above 25 cm H_2O are associated with tracheal mucosal injury. However, interventions to maintain ETT cuff pressure between 20 and 25 cm H_2O have had variable success at decreasing VAP rates.

Preventing unplanned extubations may decrease VAPs because these events are associated with an increase in VAP, probably from aspiration either at the time of extubation or at the time of reintubation. Any condensate in the ventilator circuit should be drained away from the patient in order to prevent aspiration into the ETT. The role of suctioning in preventing or causing VAP is unclear. Stimulation of cough and removal of lower airway secretions by suctioning theoretically should reduce VAP. However, suctioning may introduce bacteria and debris from the ETT intraluminal biofilm into the lower airways. Therefore, suctioning should be performed only when needed. The role of sterile saline instillation prior to suctioning is controversial with at least one study showing a reduction in the diagnosis of VAP with the use of saline instillation.

The following measures are *not* recommended because they have not consistently reduced VAP rates: prophylactic antibiotics delivered intravenously or via aerosol, intranasal mupirocin, frequent changes of unsoiled ventilator circuits or heat-moisture exchangers (HME), use of HMEs versus heated humidifiers, bacterial filters, early versus late tracheostomy, postpyloric versus gastric feeding, intravenous immunoglobulin, filgrastim, enteral glutamine, and routine chest physiotherapy. There is no reduction in VAP with the use of closed versus open suctioning systems, but closed systems may benefit the health care team by exposing them to less aerosolized secretions without adverse effect on the patient.

Several interesting technologies are under investigation, including a "mucous shaver," which removes the biofilm layer from the endotracheal tube lumen, and photodynamic antimicrobial therapy in which a particular wavelength of light is delivered to the endotracheal tube lumen while a sensitizer, such as methylene blue, is present.

Some investigators have expressed concern that elevating the HOB to between 30 and 45 degrees results in a more upright position of the ETT and trachea that could lead to an increase in leakage of material around the ETT cuff because of gravitational effects. These investigators have suggested that the prone position or the lateral horizontal position, in which the patient

is not vertically oriented, may promote drainage of secretions from the distal lung as well as diminish aspiration around the ETT cuff. Studies of these other positions have not shown consistent benefit and cannot be recommended at this time. Avoidance of the supine position is recommended.

Conventional ETT cuffs have a large volume (with diameters about 1.5 to 2 times the diameter of the trachea) and are made of PVC. As these ETT cuffs are inflated in the trachea, excess material folds over itself forming channels through which secretions can pass into the lower airway. Innovative shapes with tapering and smaller volumes, as well as materials (thin polyurethane) that do not form channels when folded over on itself, are being investigated as potentially beneficial to prevent VAP.

TREATMENT

Early initiation of empiric broad-spectrum antibiotics is imperative when VAP is suspected because both delay in initiation of treatment and inappropriate antibiotics are associated with worse outcomes. The choice of empiric antibiotics will vary depending on recent antibiotic exposure, prior culture results from the patient, known carriage of MRSA, duration of mechanical ventilation, presence of immunosuppression, severity of illness, and local susceptibility patterns (Chapter 18). Empiric antibiotics should be narrowed or stopped based on culture results and the patient's clinical course. It is reasonable to stop antibiotics on day 2 or 3 in stable patients who have negative sputum cultures, especially if new antibiotics were not started within 3 days prior to culture.

Urinary Tract Infection

EPIDEMIOLOGY, PATHOGENESIS, AND PREVENTION

Urinary tract infections (UTIs) are one of the most common causes of HAI in the ICU. Nosocomial urinary tract infections are associated with indwelling urinary catheter use in ~80% of cases. Cases in which an indwelling catheter is present are known as catheter-associated urinary tract infections (CAUTIs). The incidence of bacteriuria with an indwelling urinary catheter is 3% to 8% per day, and, as such, *duration of catheterization* is the most important risk for development of CAUTIs. Other characteristics present in many ICU patients place these patients at higher risk for developing UTI (Box 14.4).

Avoidance of unnecessary urinary catheterization is the primary means of preventing CAUTIs. Urinary catheters should be placed only when appropriate indications are met (Box 14.5), and the catheters should be assessed daily for continued need. Catheters should be removed immediately when these indications are no longer present. An estimated ~40% of continued catheter days are

BOX 14.4 ■ Risk Factors for Nosocomial Urinary Tract Infection

Use of urinary catheter
Duration of catheter use
Open drainage and collecting system (tubes, reservoir bag, and urinometer)
Errors in catheter care
Female sex
Older age
Diabetes mellitus
Microbial colonization of drainage bag or urethral meatus
Elevated creatinine

BOX 14.5 ■ Appropriate Indications for Indwelling Urinary Catheter

Urinary retention or bladder outlet obstruction
Accurate urine output monitoring required in a critically ill patient (e.g., septic shock)
Selected surgeries: urologic surgery; prolonged surgical procedures involving general or spinal anesthesia; surgery that will require large amounts of intravascular volume or diuretics
Wound care in patient with incontinence and open sacral or perineal wound who has not responded to other wound care intervention
Prolonged immobilization required (e.g., pelvic fracture and unstable spinal fractures)
Terminally ill patient with incontinence who requires catheter for comfort and in whom less invasive methods have failed and external collecting devices are not an acceptable alternative

unnecessary because of a lack of continued clinically relevant indications. Certain patients may also benefit from intermittent catheterization or non-invasive drainage catheters as an alternative for indwelling urinary catheters. Other measures to decrease CAUTI rates include proper catheter insertion using aseptic technique and use of a closed sterile drainage system. Other policies such as having only trained health care professionals insert the urinary catheters, keeping the drainage bag below the level of the bladder at all times, and avoiding opening the drainage system are also recommended. In situations where infection rates remain high despite these interventions, use of antimicrobial-coated urinary catheters may be considered.

SYMPTOMS AND SIGNS

Typical UTI symptoms for alert, uncatheterized patients include dysuria, urinary urgency and frequency, and, occasionally, flank and costovertebral angle pain. However, patients with an indwelling urinary catheter do not have dysuria and increased urinary frequency. Conversely, the catheter itself may cause discomfort in the absence of infection. In addition, many patients in the ICU also have impairments in expressing or experiencing symptoms because of altered mental status or impairments in sensation resulting from anesthesia or spinal cord injury. Additional nonspecific symptoms and signs of UTI include fever, chills, change in mental status, increased lethargy, suprapubic tenderness, and hematuria. Patients with spinal cord injury and increased bladder spasticity may have urgency and frequency without infection. No association between the presence of malodorous or cloudy urine and UTI has been demonstrated. These symptoms should not be used independently as criteria to evaluate for UTI or be used to differentiate between UTI and asymptomatic bacteriuria or colonization. Some systemic symptoms such as change in mental status, fever, and leukocytosis are difficult to attribute solely to UTI. The presence of UTI and especially asymptomatic bacteriuria may simply be an incidental finding, and other causes of symptoms or of infection should be evaluated (see Chapters 13 and 36).

DIAGNOSIS

There are various definitions for UTI, including clinical definitions (IDSA) and surveillance definitions (NHSN). The cornerstones of diagnosis of UTI are clinical evaluation supplemented by microscopic urinalysis and urine culture. In general, microscopic urinalysis is performed first, and urine culture is performed if indicated by the urinalysis. However, if the patient is severely ill and sepsis is suspected, urinalysis and urine culture should be obtained simultaneously so that empiric antibiotics can be initiated without delay. In the absence of significant immunosuppression such as neutropenia, pyuria should be present with UTI. If pyuria is not present, then typically no

additional testing should be performed. In a symptomatic patient with an indwelling catheter, the absence of pyuria suggests an alternative etiology for these symptoms. In patients with long-term catheterization, the presence of pyuria is less helpful at differentiating catheter-associated asymptomatic bacteriuria from CAUTI because pyuria can be present during asymptomatic periods and may not change significantly when symptoms are present. Therefore, pyuria alone should not be used to diagnose CAUTI in these patients.

If pyuria is present and a UTI is clinically suspected, the next step should be to obtain a specimen for urine culture. To obtain a quality urinary specimen, the indwelling urinary catheter should be removed prior to obtaining the culture, and the urine culture should be performed on a clean-catch midstream voided urine specimen, when possible. If continued indwelling catheterization is still required and the catheter was not recently placed, the catheter should be replaced prior to collecting a urine specimen for culture to avoid culturing bacteria colonizing the catheter. Some institutions repeat the microscopic urinalysis after changing or removing the catheter before sending a specimen for urine culture, but there are limited data on the use of any specific algorithm in the ICU setting.

All urine specimens should be collected using an aseptic technique. When a specimen is obtained from a catheter, it should be obtained using aseptic technique from the needleless port or, when such a port is not present, drawn from the catheter tubing using a needle and syringe. Specimens should never be taken from the drainage bag.

Although microbiologic criteria for UTI vary, typically a count of $\geq 10^3$ CFU/mL of at least one bacterial species is required to make the diagnosis of a UTI in catheterized patients. If more than two bacterial species are present, there is a high likelihood that the specimen was collected improperly and a new aseptically collected specimen should be sent for culture. Blood cultures should always be obtained in the setting of suspected systemic infection to rule out bacteremia.

TREATMENT

General Treatment Guidelines

In general, asymptomatic bacteriuria or bacteriuria in the absence of pyuria does not require antibiotic treatment and often resolves when the catheter is removed. There are certain situations when treating asymptomatic bacteriuria is indicated, including in pregnant women or in patients prior to undergoing a urologic procedure. Patients with high level of immunosuppression, including neutropenic patients, may be treated even in the absence of pyuria.

UTIs are treated with antibiotic therapy. Culture and susceptibility are useful for determining appropriate antibiotic therapy, and therapy should be adjusted to the narrowest effective agent. Duration of treatment may range from 5 to 14 days depending on the severity of infection and choice of antibiotic. Typically, 7 days of therapy is preferred in patients with a milder UTI and a longer duration of up to 14 days in those patients with urosepsis or more complicated infection (see Table 18.5, Chapter 18). Empiric antibiotic coverage should be directed against Enterobacteriaceae and *Pseudomonas aeruginosa*. In patients with severe infection or a history of colonization or prior infection with *Enterococcus* spp., empiric therapy should also be directed against *Enterococcus* spp. The presence of *Staphylococcus aureus* in the urine should raise suspicion for hematogenous seeding from a nonurinary source.

Treatment Guidelines for Candida Species

Candiduria is common in hospitalized patients and usually reflects asymptomatic colonization. Less commonly *Candida* species can cause UTI or kidney infections or may be a sign of a disseminated fungal infection. The incidence of *Candida* UTIs has been increasing, and in some ICUs *Candida* species represent the predominant organisms causing UTIs. Although not much direct mortality is associated with *Candida* UTIs, their presence is often a marker for severe underlying illness. *Candida albicans* is the single most common Candida species causing UTIs,

but many studies estimate that non-*albicans* species collectively now represent over 50% of all *Candida* urinary isolates.

To evaluate the need for treatment, the patient should be assessed for symptoms of UTI and for risk factors for development of disseminated fungal infection or ascending urinary tract infection. These risk factors include immunosuppression, diabetes, urinary tract abnormalities, urinary tract obstruction, recent urologic procedure, and the presence of urinary tract devices. In asymptomatic patients at low risk for disseminated or ascending infection, removing or changing the urinary indwelling catheter is usually all that is necessary. In some situations, treatment of asymptomatic patients is appropriate, including patients with neutropenia or planned urologic procedure.

If patients are symptomatic but at low risk for dissemination or ascending infection, one option is to change or remove the urinary catheter and then collect a repeat urine specimen and consider treatment if positive. Whenever possible, treating or eliminating predisposing conditions (control of diabetes, taper or discontinuation of steroids, and discontinuation of unnecessary antibiotics) is preferred. If these interventions fail, then antifungal therapy can be initiated as described later. If a symptomatic patient is at high risk for disseminated fungal infection or ascending urinary tract infection, then antifungal therapy should be initiated. In these patients, especially if *Candida* is isolated from repeat urinary tract isolates, the presence of a renal infection should be evaluated using appropriate diagnostic imaging. In patients with a risk of disseminated fungal infection, especially in the setting of sepsis or multiple sites with cultures positive for *Candida*, blood cultures and retinal examination are important adjunctive tests to evaluate for the presence of disseminated infection. In addition, careful skin examination for candidal lesions (pustular, papular, or necrotic) and inspection of vascular access sites for signs of infection should also be performed.

For many patients with *Candida* UTI, treatment with fluconazole is appropriate. However, many of the non-*albicans Candida* species have resistance to fluconazole. In these situations or in situations where fluconazole is contraindicated, other options include flucytosine or IV amphotericin B deoxycholate. Because of its potential toxicity and contraindication in impaired renal function, flucytosine is often avoided. Because amphotericin B is cleared renally and prolonged excretion after a single dose has been demonstrated, administration of a single dose of 0.3 to 1 mg/kg of amphotericin B is often effective for *Candida* UTIs. Another option is intravesicular irrigation with amphotericin B, which has more variable success and a high relapse rate. More complicated *Candida* genitourinary infections, such as prostatitis, pyelonephritis, or fungus balls, require a longer duration of therapy and often require surgical intervention to achieve cure. Systemic antifungal therapy may be started empirically in this setting, using amphotericin B at a dose of 0.5 to 0.7 mg/kg/day pending susceptibility data. Liposomal amphotericin B is less nephrotoxic, although its efficacy has not been as well studied.

Surgical Site Infections (SSIs)

EPIDEMIOLOGY, PATHOGENESIS, AND PREVENTION

Surgical site infection (SSI) complicates between 2% and 5% of inpatient surgeries, and in postoperative patients it accounts for 37% of nosocomial infections, resulting in significant increases in mortality, morbidity, cost, and length of stay. Most SSIs occur 7 to 10 days after surgery and are classified as either superficial incisional, deep incisional, or organ space infections (Table 14.3).

Preoperative patient-related factors increasing risk for SSI include advanced age, severity of disease, obesity, poor nutritional status, infection at distal sites, cancer, diabetes, and immunosuppression. Poor tissue perfusion and oxygenation also increase the risk for SSI. Technical risk factors for SSI include abdominal surgery, prolonged duration of surgery, wound contamination, intraoperative

TABLE 14.3 ■ **Criteria for Diagnosis of Surgical Site Infection**

	Superficial Incisional	Deep Incisional	Organ or Space
Degree of involvement	Involves only skin or subcutaneous tissue of incision	Involves muscle or fascia layers of the incision	Any area other than the incision itself that is opened or manipulated during the operative procedure
Criterion 1	Purulent drainage from the superficial incision	Purulent drainage from the deep incision but not from the organ or space component of the surgical site	Purulent drainage from a drain placed through a stab wound into the organ or space
Criterion 2	Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision	Deep incision dehisces or is deliberately opened when a patient has at least one of the following signs or symptoms: fever > 38.0° C, localized pain or tenderness (unless culture of the incision is negative)	Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ or space
Criterion 3	At least one of the following signs or symptoms of infection: localized pain or tenderness, swelling, redness, or heat, and superficial incision is deliberately opened (unless the culture is negative)	An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination	An abscess or other evidence of infection involving the organ or space on direct examination, during reoperation, or by histopathologic or radiologic examination

Presence of infection: patient must meet any *one* of the listed criteria.
Surgical site infections must occur within 30 days of the operative procedure (except in cases of deep incisional or organ-space infections involving foreign body in which the time limit is 1 year).

contamination, reoperation, poor hemostasis, emergent procedures, and insertion of drains or other foreign bodies. Hair should not be removed prior to surgery unless it will interfere with the operation. In that case, hair should be trimmed and a razor should not be used, as doing so increases the risk of SSI. In one series, infection rates varied according to wound class (Table 14.4) from 2.1% for clean wounds, to 3.3% for clean-contaminated wounds, 6.4% for contaminated wounds, and 7.1% for dirty wounds.

The use of prophylactic antibiotics reduces the risk of SSI. Prophylactic antibiotics should be administered within 1 hour before incision or within 2 hours for vancomycin and fluoroquinolones. Depending on the antibiotic chosen and its dosing schedule, the antibiotic may have to be redosed intraoperatively and continued for up to a 24-hour period. Clean wounds generally do not require prophylaxis unless the potential complications of infection would be disastrous (i.e., central nervous system operations, cardiac surgery requiring bypass, prosthesis placement). Prophylaxis is indicated for clean-contaminated and contaminated wounds. Dirty wounds generally require preoperative antibiotics when possible with continued postoperative antibiotic treatment.

TABLE 14.4 ■ **Surgical Wound Classifications**

CATEGORY	DESCRIPTION
Clean	Elective, primarily closed, no acute inflammation encountered, no entrance of normally or frequently colonized body cavities, and no break in sterile technique
Clean-contaminated	Nonelective case that is otherwise a clean, controlled opening of a normally colonized body cavity, minimal spillage or break in sterile technique, reoperation through clean incision within 7 days, negative exploration through intact skin
Contaminated	Acute nonpurulent inflammation encountered, major break in technique or spill from hollow organ, penetrating trauma < 4 hours old, chronic open wounds for grafting
Dirty	Purulence or abscess encountered or drained preoperative perforation of colonized body cavity, penetrating trauma > 4 hours old

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CHAPTER 15

Nutritional Therapy

Jennifer M. Dolan

Critical illness results in a well-orchestrated set of metabolic consequences encompassed by the terms *hypermetabolism* and *hypercatabolism.* The former refers to an increased expenditure of energy (which may be expressed as calories or milliliters of oxygen), whereas the latter refers to an increased destruction of existing tissues. When decreased nutrient intake and synthetic production are coupled with increased tissue catabolism, the normal anabolism-catabolism balance becomes severely negative (i.e., predominantly catabolic). This leads to a rapid depletion of body tissue stores and critical protein elements, such as immunoglobulins, that are characteristic of protein malnutrition.

The *goal* of nutritional therapy in the intensive care unit (ICU) is to minimize the net negative daily protein and energy balances in critically ill patients. Over time, they accumulate and evolve into net negative tissue protein and fat store balances. Providing the appropriate type and quantity of nutritional substrate partially offsets the obligatory catabolic losses in critical illness and provides fuel needed for oxidative purposes and ongoing synthetic processes.

Nutritional and Metabolic Assessment

WHEN IS THE BEST TIME TO START?

Enteral feeding should be started within 24 to 48 hours following admission to the ICU, though the nutritional status of a newly admitted patient should be assessed prior to the initiation of feeding. ICU patients with chronic diseases are often malnourished to a greater or lesser degree even before their ICU admission. With their tissue reserves already compromised, they are less able to tolerate further depletion of nutrient stores than patients who were previously well nourished. Despite the importance of determining the nutritional status of ICU patients, it remains a challenge to do so accurately because many of the traditional "nutritional assessment" parameters are unreliable when applied to the critically ill.

Body Weight

Although seemingly a straightforward measurement, body weights in ICU patients are often distorted by efforts at volume resuscitation and changing fluid distribution among various body compartments. Consequently, the patient's current weight should be compared with his or her "usual" weight as well as predicted body weight (PBW) (see formulas for PBW in Table 15.1), also referred to as lean or ideal body weight, with attention paid to estimating the "dry" weight of volume-overloaded patients.

Significant weight loss (> 10%) during the 6 to 12 months before the critical illness episode should signify a patient at high risk for clinically significant malnutrition. Despite its

Additional online-only material indicated by icon.

limitations, current weight, when compared with predicted body weight, can be used to estimate how the patient's fat calorie stores compare with normal and can guide the appropriate caloric prescription.

Serum Proteins

The profile of serum albumin, transferrin, and prealbumin, which normally gives a balanced composite view of the patient's serum protein status, is less reliable during periods of critical illness and vigorous intravascular fluid resuscitation. The reprioritization of the liver synthetic pathways and the increased catabolism of several of these proteins change them from good measures of nutritional status to prognostic indicators of severity of illness, systemic inflammation, and clinical outcomes (e.g., mortality).

Time Lines for Reaching Adequate Daily Nutrition

An equally important factor in deciding which patients should receive nutritional support is the anticipated clinical course of the current illness. When will the patient again be ingesting an *adequate* oral intake? In well-nourished patients, nutrition support should be started if no oral intake is anticipated for *greater than 5 days*. In the face of preexisting malnutrition, however, anticipation of *receiving nothing by mouth for more than 3 days* should trigger nutritional intervention. For ventilated patients, studies suggest that nutritional therapy should start within 24 to 48 hours of ICU admission unless contraindicated. Consensus guidelines recommend that efforts to provide > 50% to 65% of goal calories be made over the first week in order to achieve the clinical benefit of enteral nutrition (EN). However, more recent data from the EDEN randomized trial of patients with acute lung injury on ventilators showed that providing trophic EN (i.e., providing ~25% of recommended daily nutritional goals) for the first 6 days of ventilation resulted in similar clinical outcomes as in those who received 80% of full goal.

Caloric Goal Delineation

Delineation of realistic clinical goals is important in order to prescribe appropriate cost-conscious prescriptions for total parenteral nutrition (TPN) or total enteral nutrition (TEN). To make a rational *caloric prescription*, one needs to know the individual patient's total energy expenditure (TEE) as well as the patient's caloric tissue goals. TEE defines the severity of hypermetabolism. TEE can be estimated by indirect calorimetry in many ICU patients but not those on ventilators with high inspired oxygen concentrations ($FiO_2 > 0.6$) and positive end-expiratory pressure (PEEP) of 7.5 to 10 cm H_2O since the measurement depends on the patient being able to tolerate a brief interruption of ventilation. In the ICU patient on bed rest, resting energy expenditure (REE) measured over 30 minutes generally approximates TEE. After determining TEE, the caloric (or "nonprotein" energy) prescription is guided by the clinician's goal for the patient's fat stores (Table 15.1).

If indirect calorimetry is not feasible, REE can be estimated by using the Harris Benedict or the Penn State equations with "multipliers" to take into account the hypermetabolic effects of critical illness (see online Table 15.E1). Some intensivists use an even simpler "one-size-fits-all" rule, such as providing 25 kcal/kg PBW. Even with the adjustments, these rules can still under- or overestimate actual TEE in hypermetabolic states, emphasizing the desirability of indirect calorimetry measurements if possible and the need for regular monitoring of the patient's response to nutritional therapy as discussed further on.

Protein Goal Delineation

During critical illness, protein is mobilized from many body tissues, such as the intestinal tract, skeletal muscle, albumin mass, and the skin. This provides precursors for crucial protein synthesis (e.g., acute-phase plasma proteins and immunoglobulins), wound healing, and for energy if other substrates are not readily available. The magnitude of this mobilization and redistribution can be

TABLE 15.1 ■ **Caloric Prescriptions Based on Body Weight and Status of Fat Stores**

Current Body Weight Versus Predicted Body Weight*	Inferred Status of Fat Stores	Caloric Prescription
CBW < 90% PBW Or BMI < 18.5 kg/m^2	Subnormal	One should use sufficient energy supply to replete depleted fat stores (daily caloric supply > REE)
CBW 90%–130% PBW Or BMI 18.5–29.9 kg/m^2	Normal	The caloric prescription is designed to maintain the fat stores (daily energy supply = REE)
CBW >130% PBW Or BMI ≥ 30 kg/m^2	Excessive	Energy supply should be designed to partially utilize the excess fat stores; to do this, supply ~50% REE as nonprotein calories and 2 g protein/kg/day, assuming normal renal and hepatic function

*CBW is the best estimate of the patient's current "dry" body weight (e.g., before volume resuscitation); predicted (or lean or ideal) body weight (PBW in kg) for males = 50.0 + 2.3 for each inch above 60 in height and for females = 45.5 + 2.3 for each inch above 60 in height.

CBW, current body weight; PBW, predicted body weight; REE, resting energy expenditure, which approximates total energy expenditure in ICU patients.

impressive, with urinary nitrogen losses of 30 to 50 g/day typically observed in patients with multiple trauma or severe sepsis or after bone marrow transplantation. *This represents a loss of greater than 1 kg of lean tissue each day* (with loss of 30 g of lean tissue being roughly equivalent to loss of 1 g of nitrogen). Endogenous production of glutamine from skeletal muscle may become insufficient, making this generally nonessential amino acid conditionally essential.

Although the catabolic process that is induced by inflammatory mediators cannot be reversed by providing exogenous protein (i.e., the latter cannot per se make the patient's nitrogen balance positive), the magnitude of the protein loss can be diminished by providing protein and energy substrates during periods of critical illness. Some chronically critically ill patients who have evidence of inadequate growth hormone action have responded favorably to brief courses of growth hormone. However, the Food and Drug Administration recommends against the use of growth hormone based on an increased risk of mortality, nosocomial infection, and organ dysfunction in critically ill patients supplemented with growth hormone.

Determining how much protein to provide by nutritional therapy should, in general, be *independent* of one's total (nonprotein) caloric prescription (described earlier). How much protein to give to a critically ill ICU patient initially remains more or less an empirical decision. One acceptable approach for these circumstances is to give 2 g of protein/kg current body weight (assuming normal functioning hepatic and renal disposal systems [Table 15.2]). For sick but not critically ill ICU patients, daily protein administration on the order of 1.5 g/kg/day would be an appropriate starting point. In comparison, recommended daily protein intake for healthy, well-nourished adults is only on the order of 0.8 to 1 g/kg/day.

The degree of protein catabolism and effects of the daily protein prescription on this loss can be monitored by serial measurements of the patient's nitrogen balance. When calculating nitrogen balance, one should account for changes in blood urea nitrogen (BUN) and fecal nitrogen loss as shown in the equation:

$$\text{Nitrogen balance} = \text{Nitrogen intake (g)} - [\text{Urinary Nitrogen (g)} + \Delta\text{BUN (g)} + 4]$$

where ΔBUN (in g) = [0.6 x weight(f) x BUN(f)] − [0.6 x weight(i) x BUN(i)], BUN(i) and BUN(f) are the initial and final values of blood urea nitrogen (BUN expressed in g/L–not the laboratory output of mg/dL) and weight(i) and weight(f) are the initial and final weights (in kg)

TABLE 15.E1 ■ **Estimates for Daily Caloric and Protein Needs**

For Caloric Needs (Total Kcal) for Weight Maintenance (Harris-Benedict Formulas)

For Males

[65.5 + 13.7 × weight (kg) + 5 × height (cm) – 6.7 × age (y)] × Activity Factor* × Injury Factor†

For Females

[665.1 + 9.6 × weight (kg) + 1.8 × height (cm) – (4.7 × age (y)] × Activity Factor* × Injury Factor†

For Protein Needs

Protein = 2–2.5 gm/kg or a ratio of Kcal:nitrogen (g) of 100:1

*Activity Factor	
Confined to bed	1.2
Ambulatory	1.3
Fever	1.13 for each ° C greater than 37.0° C

†Injury Factor	
Surgery	1.1–1.2
Infection	1.2–1.6
Trauma	1.4–1.8
Sepsis	1.4–1.8
Ventilator	1.3
Skin breakdown	1.3–1.5
Radiation therapy or chemotherapy	1.6
Burn injury	
< 20%	1.2–1.4
20%–25%	1.6
25%–30%	1.7
30%–35%	1.8
35%–40%	1.9
40%–45%	2.0
> 45%	2.1

Data from Long CL, Schaffel N, Geiger JW, et al: Metabolic response to injury and illness: estimation of energy and protein needs from indirect calorimetry and nitrogen balance. JPEN 3:452-457, 1979; Gottschlich MM, Matarese L, Shonts E (eds): Nutrition Support Core Curriculum. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition (ASPEN) Publishers, 1992; and Williamson J: Actual burn nutrition care practices: a national survey (Part II). J Burn Care Rehab 10:185-941, 1989.

TABLE 15.2 ■ **Adjustments to Nutrition Prescription with Organ Dysfunction**

Organ Dysfunction	Adjustments
Cardiac	
	1. ↓ Sodium
	2. ↑ Potassium for patients on digoxin
	3. Increased need for potassium, magnesium, and zinc with diuresis
	4. Use maximally concentrated solutions
	5. Thiamine supplementation in patients with heart failure
Hepatic	
	1. Provide at least 150 g of glucose per day
	2. Use mixed fuel system (glucose and fat)
	3. ↓ Protein if encephalopathy occurs or worsens
	4. Use modified amino acid (AA) formula (high branched-chain AA) if patient's encephalopathy is unresponsive to medical treatment or worsens with standard AA formula
	5. Maximally concentrate all solutions
Renal	
	1. ↓ Calories for patient on peritoneal dialysis (see Chapter 20)
	2. ↓ Fat kilocalories with elevated triglyceride levels
	3. ↓ Protein if blood urea nitrogen > 100 mg/dL
	4. ↓ Magnesium, potassium, and phosphorus
	5. ↑ Acetate
	6. Maximally concentrate all solutions
Respiratory	
	1. Avoid overfeeding to prevent excessive CO_2 production
	2. Feed at the measured energy expenditure
	3. Maximally concentrate all solutions

Adjustments to standard formulas: arrow up, increase; arrow down, decrease.

during the measurement period, respectively. Urinary nitrogen (in g) is measured as the concentration of urea in urine multiplied by the volume of a 24-hour urine collection.

For the purposes of the equation, 6.25 g of protein is assumed to be equivalent to 1 g of nitrogen so that nitrogen intake equals protein intake (in grams) divided by 6.25. The "4" in the equation represents normal fecal (and other nonurinary) nitrogen loss (4 g/24 hours). This may be, on the one hand, much less (close to zero) if the patient is on TPN and has no stools or, on the other hand, much more (double or triple) if the patient has diarrhea, an enterocutaneous fistula, or a wound vacuum manager. Wound vacuum drainage is equivalent to 2 g of nitrogen per liter.

Providing Nutritional Support

SELECTING THE ROUTE OF ADMINISTRATION

After determining that nutritional support is required, defining its goals, and writing the calorie and protein prescriptions for the patient, one must select the most appropriate route of administration. This decision, however, should not be dictated simply by what access the patient currently has available.

Enteral nutrition is strongly preferred if the gastrointestinal (GI) tract (from the jejunum distally) is functional and accessible without contraindications to its use. The potential benefits of using the GI tract relate to prevention of mucosal atrophy and its associated impairment as a barrier for bacteria and their products, the avoidance of the known and potential complications associated with TPN, and reduced cost compared with TPN.

Success in using the GI tract often depends on the intensivist's motivation and ability to assess its functional status accurately. The latter is usually based on the following five parameters: (1) stool output, (2) nasogastric tube output, (3) nausea or vomiting, (4) findings on abdominal examination, and (5) findings on radiologic examination. Some centers have avoided enteral feedings in patients in shock because of the risk of worsening gut ischemia during periods of compromised gut blood flow. However, other centers use enteral feedings in ICU patients even when on low to moderate doses of vasopressors. Support for the latter comes from the 2012 EDEN randomized trial, which reported no adverse outcomes attributed to enteral feeding of patients in nonrefractory shock. (EDEN excluded patients in refractory shock, defined generally if receiving high dose vasopressors, e.g., norepinephrine infusion ≥ 30 mcg/min.)

If enteral therapy cannot be initiated or has failed, the parenteral route should be selected. Even after parenteral therapy has started, it is important to reassess the GI tract periodically and attempt enteral feeding if feasible. *Dual modality therapy* refers to using the enteral route at a lower fraction (e.g., ≤ 25%) of daily nutrient goal to prevent mucosal atrophy while using the parenteral route to provide the majority of the daily nutrient goals.

Whatever the route, there must be constant attention to therapy tolerance and a quick response in switching patients from one route to another as necessary. The two approaches should be regarded as complementary, not competitive.

ENTERAL NUTRITION

In general, there has been renewed interest among intensivists in providing nutritional support enterally. Improved enteral access devices and technologic advances in enteral formulas and delivery systems have resulted in improved success in meeting the patient's daily nutrient goals during critical illness.

Enteral Access

Enteral nutrition can be administered through a variety of tubes either into the stomach (i.e., the tip of the feeding tube is prepyloric) or into the small intestine (i.e., the tip is postpyloric) (Chapter 16). Determining which type of enteral feeding to pursue is influenced by several factors: gastric motility, continuity of the GI tract, and the risk of aspiration. The type of tube (temporary versus permanent) depends on the anticipated length of therapy, with temporary enteral access generally preferred if the need for nutritional support is anticipated to be less than 1 month.

Whether enteral feedings should be delivered pre- or postpylorically remains controversial, and local practices tend to reflect, to a large degree, the preferences of individual ICUs and institutions. Although it makes good clinical sense that intragastric feedings should be avoided in patients with a high risk for aspiration, prospective clinical trials comparing pre- and postpyloric placement in ICU patients to show one or the other approach having better outcomes are lacking. Retrospective data show that, as compared with the stomach, the percentage of aspiration is progressively lower in patients with tubes that empty into the first through fourth portion of the duodenum and beyond. Regardless, morbidity and mortality data support the use of early enteral nutrition rather than specific location of the feeding tube's tip, so delay in starting enteral nutrition in an effort to obtain postpyloric access is not recommended.

In contrast, several controlled studies of ICU patients document the benefit of elevating the head of the bed to 30 to 45 degrees for all patients receiving enteral feeding. Parenthetically, this

position should also be standard ICU practice for those not receiving such feedings (unless contraindicated) because this simple maneuver is effective in preventing aspiration and ventilator-associated pneumonia (see Chapter 14).

Placing the tip of a nasoenteral feeding tube in a postpyloric location can be aided by the use of pharmacologic agents (metoclopramide or erythromycin) or radiologic placement with fluoroscopy to ensure postpyloric placement. This can be performed at the bedside without undue delay in most ICUs (Chapter 16). If performed routinely, it eliminates the downtime associated with waiting for tube passage and encourages an early start of enteral feeding.

Small-bore nasoenteral feeding tubes may become lethal weapons, however, when they are inserted with a wire stylet in obtunded or intubated ICU patients because they may pass into the trachea in these patients by mistake (Chapter 16). These tubes tend to track alongside the patient's endotracheal tube, which results in inadvertent placement into the trachea. If a tube with a stylet passes into the trachea of intubated patients, it has sufficient stiffness to perforate the visceral pleura readily on further advancement. The resulting tension pneumothorax can have disastrous results. For this reason, some ICUs ban the use of stylets for insertion of these feeding tubes altogether. Other ICUs mandate fluoroscopic guidance (supervised by experienced clinicians) during insertion of these tubes with stylets. As an additional precaution against passing the tube into the trachea, some ICU clinicians view the lateral neck fluoroscopically at the bedside to confirm the posterior location of the feeding tube in the esophagus. However, no method can guarantee proper placement and abdominal radiographs should be routinely obtained to confirm proper location of the tip.

Selection of the Enteral Formula

The selection of an appropriate enteral formula involves choosing a formula that best meets the patient's daily caloric and protein requirements.

The composition of enteral formulas has changed dramatically over the years with advances in both quantity and quality of substrate. Because the majority of critically ill patients do not have severe impairment of the digestive and absorptive functions of the GI tract, most generally tolerate formulas with intact proteins. Many specialty formulas target specific organ dysfunction. Although the outcomes data supporting the efficacy of these formulas (and hence justifying their extra cost) are controversial, the type and degree of organ dysfunction should be taken into account when providing enteral nutrition (see Table 15.2).

Delivery and Administration of Enteral Nutrition

Enteral nutrition can be administered intermittently or continuously. Intermittent infusions generally have larger volumes (150 mL to 500 mL) delivered periodically (every 4 to 6 hours) during the day. Continuous infusions deliver smaller volumes (50 mL to 150 mL/hour) over 12 to 24 hours. The position of the feeding tube tip is the major determinant of the method of administration. When enteral feeding is delivered into the small intestine, it should only be administered continuously via an infusion pump to reduce the possibility of intolerance, such as diarrhea or abdominal distention. Enteral delivery schedules during periods of critical illness are typically for 24 hours. Reducing the duration of infusion (by increasing the rate) is appropriate if there are frequent interruptions to the infusion during the day or if one wants the patient to be relatively free of the feeding apparatus during daytime activities—for example, to do physical therapy during the acute or recovery phase.

Intermittent feeding is typical when the enteral feeding tube tip is in the stomach. Although this may be optimal for an ambulatory patient, during critical illness a slower continuous infusion may be better tolerated. It is unclear whether continuous delivery of gastric feedings reduces or increases the risk of aspiration compared with intermittent delivery in ICU patients.

Complications of Enteral Feeding

Mechanical complications relating to surgical enteral access can occur at the time of insertion or during the postoperative maintenance and care of the device. Ensuring that the tube is properly secured can prevent problems with peritubular leakage and tube migration. Tube obstruction can be minimized with attention to flushing protocols and avoidance of medications delivered via the small-bore tubes. Using at least a 12 Fr (French) diameter tube lumen (with 14 Fr preferred) helps prevent occlusions. Erythromycin, metoclopramide, or combination therapy may be effective in treating feed intolerance evidenced by high gastric residual. If high gastric residual persists despite medical management, insertion of a postpyloric feeding tube (or a combination "G-J tube" in which the gastric [G] tube is used to drain the stomach of its gastric fluid to prevent aspiration and to administer "oral" medications while the postpyloric jejunal [J] tube is used for feeding) is suggested for ongoing nutritional support. Avoiding the delivery of hyperosmolar medication and maintaining a closed delivery system can prevent GI complications such as diarrhea. If significant diarrhea (> 500 mL/day) occurs and *Clostridium difficile* is ruled out or treated (see Chapter 38), one should provide antidiarrheal agents, such as loperamide (Imodium), on a routine schedule.

PARENTERAL NUTRITION

Indications and Specifications

Parenteral nutrition should be used if the GI tract is nonfunctional because of dysmotility, disrupted continuity, ischemia, or obstruction or if enteral nutrition supply cannot be consistently and adequately achieved. Although controversial, some centers also avoid enteral nutrition if the patient remains hypotensive (i.e., mean arterial pressure < 60 mm Hg) due to shock or is on high dose vasopressors.

Calories are supplied with either dextrose or fat emulsions. Dextrose usually provides 50% to 70% of the daily nonprotein calorie supply, but dextrose should not exceed 5 g/kg estimated dry weight/day. The latter is an approximation of the body's oxidative limits during critical illness. Exceeding this guidepost often leads to the storage of excess calories as fat in the liver. Overfeeding of calories can be diagnosed by measuring the respiratory quotient (R.Q.) (i.e., the ratio of CO_2 production to O_2 consumption measured by indirect calorimetry) and finding that the R.Q. exceeds 1.

The other major caloric fuel is fat, which, in critically ill patients, can obviate the negative effects of excess carbohydrate infusion. Most practitioners supply 30% to 50% of the daily caloric requirement as fat and limit the total dose to 1 g/kg/day. The most common type of lipid used as a caloric source in TPN is long-chain triglycerides in a lipid emulsion derived from soybean or safflower oil. Long-chain triglycerides may exert negative effects on neutrophil function and macrophage phagocytosis. They also seem to result in a general impairment in the function of the reticuloendothelial system as a result of lipid particles being trapped in the reticuloendothelial cells, partially disrupting their function. The clinical relevance of these effects, however, is still controversial but emphasizes that the decision to begin TPN should not be automatic. It should be made only after weighing the balance between potential benefits and potential harms. Omega-3 fatty acids have a lower inflammatory profile than omega-6 fatty acids, but they are not available for use parenterally in the United States.

The normal vehicle to supply protein is synthetic crystalline amino acid solution available in concentrations ranging from 1% to 15% (a mix of essential and nonessential amino acids). Although giving intravenous supplementation with glutamine has been regarded as standard care for ICU patients receiving parenteral nutrition (primarily on the basis of meta-analyses that indicated a lower risk of death with such supplementation), a large multicenter randomized controlled clinical trial published in 2013 by Heyland et al found that ICU patients with multiorgan failure who were given glutamine had a significantly increased risk of in-hospital mortality

and at 6 months. These results raise concerns and questions about the efficacy and safety of IV glutamine supplementation in ICU patients, especially those with two or more organ failures.

Vitamins and Trace Elements

During acute periods of stress and accelerated metabolic demand, there may be an increased need for vitamins and trace elements, but how much of an increase is needed has not been clearly defined. If stores are depleted from a prolonged chronic illness before the onset of acute illness, deficiencies may exist even if serum levels appear normal. In addition to standard multivitamin preparations, vitamin K (1 mg) is added daily to TPN solutions to provide maintenance needs. Giving TPN without adequate thiamine has resulted in cases of severe lactic acidosis when multivitamins for TPN were temporarily in short supply in the United States.

Maintenance of parenteral iron is generally not recommended during periods of critical illness because parenteral iron dextran is not compatible with lipids, preventing its being added to lipid-containing TPN solutions. Trace elements are required during periods of increased metabolic demands and can be delivered to the critically ill patient by daily addition to TPN.

Effects on Fluid and Acid-Base Balance and Glucose Homeostasis

During periods of critical illness, a multitude of factors contribute to the patient's fluid balance and electrolyte homeostasis. For example, during acute injury, there is an initial period in which there is sodium and water retention. In essence, TPN is a carbohydrate-lipid-protein–enriched fluid and electrolyte solution that can be modified appropriately to treat fluid and electrolyte disorders as well as to provide nutrition.

Maximally concentrating all solutions in the critically ill patient avoids premature discontinuation of TPN when the patient's fluid status changes quickly—for example, when he or she can no longer tolerate the same volume of fluid in the TPN prescription. Acute increments of volume can be achieved with intravenous "piggybacks."

Acid-base balance is of critical importance during periods of severe illness. The TPN solution itself contributes minimally to the disruption of acid-base balance. For example, TPN solutions designed for central venous administration generally have a pH in the range of 4 to 5. This pH is increased somewhat with the addition of lipids, and any residual acidity is balanced by the addition of base in the form of acetate (as the sodium or potassium salt).

Blood glucose control can be particularly labile during periods of severe illness, and hyperglycemia may be exacerbated by TPN administration. The use of a mixed fuel system (which delivers a combination of lipid and dextrose calories) generally eases the demand for exogenous insulin. If needed, insulin should be added to the parenteral nutrition in a quantity sufficient to cover the dextrose content of the parenteral nutrition only. An insulin drip should be used to manage medically related hyperglycemia. Although the initial single-center report that a more intensive insulin therapy (target blood glucose of 80 to 110 mg/dL) was shown to reduce mortality among critically ill surgical ICU patients compared to a regimen with a target glucose of 180 to 210, subsequent studies of medical and surgical ICU patients have not replicated those results. Large multicenter studies of both surgical and medical ICU patients showed either an increased mortality or no significant effect on mortality of the studied populations. Furthermore, virtually all of these latter studies documented an increased risk of severe hypoglycemia (≤ 40 mg/dL) with an intensive insulin therapy with a target blood glucose of 81 to 108 mg/dL (4.5 to 6 mmol/dL) compared to a conventional, less intensive regimen with target ranges of ≤ 180 mg/dL (10 mmol/L or less) (Chapter 12).

Central Venous Access

Central venous access is mandatory to deliver TPN solutions safely and efficiently because these solutions are calorically dense, contain large amounts of nitrogen, and must often be prepared

in a minimal volume, resulting in remarkable hypertonicity (> 900 mmol/L). The catheter tip for delivery of TPN should be positioned in the superior vena cava to prevent development of thrombophlebitis as a complication. Insertion of central venous catheters using maximal barrier precautions and meticulous nursing care of the insertion site afterward is crucial to minimize the risk of infectious complications in patients receiving TPN. Furthermore, one port of the central access should be dedicated to TPN administration only (see Chapters 11 and 14).

Impaired "Disposal Systems"

The "disposal systems" of the body handle the end products of metabolism. Impairments in this functional capacity of the renal, hepatic, and respiratory systems are common in the critically ill. When one or more of these systems are impaired or when there is cardiac failure, the prescription for TPN nutrients or their means of delivery or both should be adjusted (Table 15.2).

Measuring Nutritional Goal Achievement

SERIAL MARKERS TO MEASURE

It is important to monitor patients to determine whether the delivery of nutritional support is achieving its goals. To this end, serial measurements of body weight should be made. As a rule, body weight changes over several weeks should reflect tissue accretion or depletion, so increased "dry" body weight is an important measure of nutritional goal achievement.

To determine whether the energy prescription reflects the changing metabolic state of the patient, it is important to obtain serial measures of REE. One should also regularly assess measures of nitrogen balance and protein stores (see the equation presented earlier). A realistic nitrogen balance goal in a critically ill patient, however, is not to achieve a positive balance but rather to *reduce* the negative nitrogen balance. Serial serum proteins, such as albumin, transferrin, and prealbumin, reflect not only changes in the visceral protein compartment over time but also their rates of synthesis and degradation, which are markedly affected by the presence of critical illness. Nonetheless, changes in these plasma proteins have considerable prognostic significance.

REASONS FOR UNDERACHIEVEMENT OF GOALS

The main reasons for not achieving nutritional goals are logistical in nature—for example, no available access, fluid restrictions, or decreased clearance through disposal systems. Most of these causes are preventable if an aggressive approach is employed to encourage a timely start and to monitor the effectiveness of parenteral or enteral therapy. Evidence-based nutrition support feeding protocols promote earlier feeding and greater nutritional adequacy.

Clinical Pearls and Pitfalls

1. Diarrhea often occurs in ICU patients receiving enteral feedings, which is rarely solely caused by the feedings but more often is associated with medication delivery or GI malabsorption or infection (see Chapter 38).
2. High gastric residual may preclude provision of adequate enteral nutrition support; in this case, consider postpyloric enteral feeding.
3. If the patient with a nasoenteral feeding tube in place postpylorically has an episode of vomiting, one should confirm that the tip of the tube is still postpyloric because reverse peristalsis may displace it into the stomach.
4. Be aware of the "refeeding syndrome" when starting nutritional therapy in severely malnourished ICU patients (see "Phosphate Disorders" in Chapter 39).

5. Consider excessive production of CO_2 resulting from overfeeding of calories while trying to wean patients with limited ventilatory capacity. If overfeeding is present, indirect calorimetry will demonstrate a respiratory quotient greater than 1.

An annotated bibliography can be found at www.expertconsult.com.

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Heyland D, Muscedere J, Wischmeye PE, et al: A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med 368:1489-1497, 2013.

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This large (> 6000 ICU patients) multicenter randomized controlled trial, the NICE-SUGAR study, reported that intensive glucose control increased mortality in ICU patients treated with a blood glucose target of 81 to 108 mg/dL compared to those treated with a target of 180 mg/dL or less. These results were opposite those of earlier single center studies that showed improved mortality with similar intensive glucose control in surgical and medical ICU patients.

Takala J, Ruokonen E, Webster NR, et al: Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med 341:785-792, 1999.

These authors reported the results of two randomized placebo-controlled clinical trials of high dose growth hormone in critically ill patients both of which showed a markedly increased risk of death in the growth hormone treated patients.

CHAPTER 17

Pharmacokinetic Alterations in the Critically Ill

Amanda M. Ball ■ Cassandra J. Bellamy

The pharmacokinetics of many drugs may be substantially altered in critically ill patients. Appropriate dosing of a specific drug requires an understanding of how abnormal physiology caused by critical illness or by the common interventions performed in the intensive care unit (ICU) may change the drug's pharmacokinetics (i.e., the time course of a drug's concentration in blood and other body fluids) and pharmacodynamics (i.e., the time course of a drug's effects on the patient). This chapter emphasizes medications commonly used in the critically ill and specific pharmacokinetic or pharmacodynamic alterations.

Effects of Altered Physiology on Pharmacokinetics

CARDIOVASCULAR DISORDERS

Acute decreases in cardiac output diminish organ blood flow and may impair drug clearance. Absorption of orally administered drugs may also be decreased in patients with congestive heart failure.

HEPATIC DYSFUNCTION

Disorders of the liver can impact hepatic metabolism of medications differently depending on the type and degree of dysfunction. In general, patients with hepatic disease have a decreased clearance of medications that are hepatically metabolized, with those that undergo hepatic oxidation more severely impaired than those that undergo hepatic conjugation. Patients with hepatic disorders are commonly hypoalbuminemic and may also have increased volumes of distributions of highly protein bound drugs (because of the increased distribution of free drugs in all body fluids, including ascetic fluid). In hypovolemic patients, perfusion of the liver may be compromised, resulting in decreased drug clearance. Drugs that undergo extensive enterohepatic recirculation may also have increased oral bioavailability because of the decreased hepatic metabolism. Generally, hepatic metabolism of drugs is decreased to a greater extent in patients with more severe hepatic dysfunction.

RENAL DYSFUNCTION

Although low-molecular-weight drugs (that are not highly protein bound) are filtered at the glomerulus and then partially reabsorbed, most drugs eliminated by the kidney are secreted. The dose or interval of drugs eliminated renally by either mechanism must be changed when renal function is impaired. Renal clearance of medications decreases in proportion to decreases in creatinine clearance (CrCl).

DIALYSIS

Whether a drug is affected by hemodialysis depends on the drug's physicochemical properties and the method of hemodialysis. In general, highly water-soluble drugs are more dialyzable than are water-insoluble drugs. Drugs with large molecular weights, large volumes of distribution (>2 L/kg), and extensive protein binding are not removed by conventional intermittent hemodialysis with low flux filters; however, high-flux dialysis may remove larger molecules. Currently, the majority of patients receive hemodialysis with high-flux filters. In addition to the physiochemical properties of a medication, the amount of drug removed by hemodialysis depends on the length of the hemodialysis session, the rate of blood flow, and dialysate. Patients receiving ultrafiltration will have lower percentages of drug removal than those receiving hemodialysis. If a medication is significantly removed by hemodialysis, patients may require a supplemental dose following the dialysis session. Continuous renal replacement therapy uses membranes that are similar to high-flux filters and approximates a CrCl of 30 to 60 mL/min depending on rate of blood flow and dialysate (Chapter 20). Medications in these patients should be adjusted accordingly.

FLUID STATUS CHANGES

Hypovolemia concentrates extracellular solutes, including drugs, and may reduce renal drug clearance. In addition, hypovolemia and shock decrease hepatic blood flow, which, in turn, reduces hepatic drug metabolism. In contrast, fluid overload lowers plasma drug concentrations, especially for highly protein bound and water-soluble drugs.

MALNUTRITION

In protein-depleted states when the total serum drug concentration is within the therapeutic range, the unbound (free) fraction of highly protein bound drugs—for example, drugs binding to albumin—will be increased and may result in toxic effects. Thus, therapeutic levels of such a drug (reflecting the total serum concentration) will underestimate its potential for toxicity in malnourished patients. Free concentrations of highly protein bound medications with narrow therapeutic indices should be obtained in these patients. Severely malnourished patients may also have decreased hepatic drug metabolism.

OBESITY

A relatively new challenge in health care is the management of patients who are overweight, obese, or morbidly obese (Chapter 29). Although this represents a growing proportion of patients, information regarding the pharmacokinetic changes in these patients is scarce. Information about the oral absorption of medications in obese patients is lacking, and it is unclear what changes occur in this population, if any. Patients undergoing gastric bypass represent an understudied population in regard to oral absorption of medications. No conclusion regarding altered absorption in this population can be made. Obese patients commonly have increases in cardiac output, total blood volume, and organ mass. These changes theoretically contribute to an increased volume of distribution; however, the clinical significance of this is unknown. Serum albumin and total protein are not altered in obese patients, thus distribution of medications that are significantly bound to plasma proteins should not change. Medications that are highly lipophilic may have higher volumes of distribution; however, not all lipophilic drugs distribute to adipose tissue. The decision of dosing a medication on a predicted or lean (also referred to as "ideal"), total, or adjusted body weight should be based on published clinical data. In general, the metabolism of drugs that

undergo phase II conjugation may be increased, whereas the metabolism of drugs that undergo phase I metabolism can vary based on the specific cytochrome P450 enzyme involved.

Clearance of drugs dependent on glomerular filtration is significantly higher when compared to normal-weight subjects. Estimating the glomerular filtration of the obese patient is challenging, and common calculations for estimating CrCl may underestimate glomerular filtration.

THE ELDERLY ADULT POPULATION

As the elderly adult population increases, it has become increasingly important to evaluate the use of medications within this population, including pharmacokinetic changes that may occur with normal aging. Although the technical definition for an elderly patient is a person 65 years or older, not all patients in this age category will exhibit the same pharmacokinetic changes. Variations in underlying health and comorbid states will affect pharmacokinetics to a greater extent than an absolute age. In general, elderly patients have elevated gastrointestinal pH, potentially impairing absorption of medications that are acid dependent. Elderly patients may also have delayed gastric emptying, which may decrease the rate but not the overall absorption of medications. Changes in body composition such as a decrease in lean muscle mass and a relative increase in adipose tissue commonly occur in these patients. Because of these changes, medications that are distributed to adipose tissue may have increased volumes of distribution and medications that are water-soluble may have decreased volumes of distribution. As patients age, the ability to metabolize drugs via hepatic oxidation is reduced, whereas the ability to metabolize those that undergo hepatic conjugation is comparatively well preserved. This decline in hepatic function may result in an increase in oral bioavailability of drugs with extensive first pass metabolism. A decrease in glomerular filtration commonly occurs as a patient ages and is closely correlated to increasing age. Medications that are eliminated by glomerular filtration will therefore require dosage reductions. Furthermore, certain medications that are unsafe to administer at reduced creatinine clearances may even be contraindicated in the elderly. There are numerous calculations for estimating CrCl in patients; however, no standard exists for the elderly. When using narrow therapeutic index medications, renal function should be carefully assessed, as many calculations will overestimate CrCl in the elderly population.

MECHANICAL VENTILATION

Hemodynamic depression from mechanical ventilation may impair liver and renal function, especially in patients with high levels of applied positive end-expiratory pressure (PEEP) or auto-PEEP (>10 cm H_2O) and large tidal volumes (>10 mL/kg predicted body weight). Decreases in cardiac output may occur without hypotension.

TRANSDERMAL DRUG DELIVERY

The drawbacks of the administration of medications via the transdermal route should be carefully considered in the critically ill population. Decreased perfusion to subcutaneous and epidermal tissue may make absorption erratic and unreliable for drug administration. Furthermore, certain medications such as fentanyl have increased absorption in febrile states, which may lead to adverse events from unpredictable drug administration. Certain other drugs (nicotine, clonidine, Androderm, or scopolamine) have patches with aluminum in their backing such that they may not be worn in a magnetic resonance imaging (MRI) machine or during cardioversion. Rapid escalation or de-escalation of dose is typically not possible because of the longer onset and offset of transdermal medications. Overall, caution should be used when choosing transdermal medications, and other more reliable routes of medication administration should be chosen when possible.

AMINOGLYCOSIDES

Aminoglycoside antibiotics inhibit bacterial protein synthesis through irreversible binding to 30S ribosomal subunits. Amikacin, gentamicin, and tobramycin have activity against most gram-negative bacteria and are commonly administered parenterally for health care associated infections. Neomycin, the only orally available aminoglycoside, has poor bioavailability and is primarily used for hepatic encephalopathy or gut decontamination. When administered parenterally, aminoglycosides are rapidly distributed (30 minutes to 1 hour), mainly to extracellular body fluid, resulting in a small volume of distribution (0.15 to 0.35 L/kg). Aminoglycosides are excreted through glomerular filtration with elimination half-lives closely correlated to CrCl. In a patient with normal renal function, the elimination half-life is between 2 and 3 hours; however, this is dramatically increased in patients with renal insufficiency.

Aminoglycosides exhibit antibacterial activity through concentration-dependent killing, meaning that the ability to kill bacteria improves with increasing concentrations. The optimal pharmacodynamic parameter associated with aminoglycoside bactericidal activity is a peak-to-minimum inhibitory concentration (peak: MIC) ratio of 10:1. Several dosing strategies, including traditional (multiple daily dosing) and once-daily dosing, can be used to achieve this goal, although once-daily dosing has become more common. This dosing strategy maximizes peak concentrations, and thus bactericidal activity, while potentially minimizing toxicity by allowing for aminoglycoside free intervals. The result is a decrease in the risk for trough-related toxicities (nephrotoxicity).

Aminoglycosides, specifically gentamicin, are also used for synergistic effects against gram-positive organisms (*Staphylococcus* spp., *Enterococcus* spp., and *Streptococcus* spp.). The dosing strategy and goal peak concentrations for synergy differ from those associated with managing infections due to gram-negative bacteria. Table 17.1 contains dosing strategies and goal serum concentrations for traditional, once-daily, or extended interval and synergy dosing. Peak and trough concentrations are typically recommended for patients receiving traditional or synergy

TABLE 17.1 ■ **Dosing Strategies and Desired Therapeutic Concentrations for Aminoglycosides**

Aminoglycoside	Dose (mg/kg)*	Goal Peak (mg/dL)†	Goal Trough (mg/dL)	Dosage Interval‡
Dosing Strategy: Traditional				
Gentamicin/ tobramycin	1.7–2.5	4–10	<2	8–24
Amikacin	7.5	15–0	<8	12–48
Dosing Strategy: Synergy				
Gentamicin	1§	3–5	<2	8–24
Dosing Strategy: Once Daily (Extended Interval)‖				
Gentamicin/ tobramycin	5–7	NA	See nomogram	24–72
Amikacin	10–15	NA	See nomogram	24–72

*If actual body weight (ABW) > 120% of predicted body weight (PBW), use adjusted body weight (AdjW) where AdjBW = (ABW – PBW) * 0.4 + PBW. Note: PBW (kg) for men = 50 + 2.3 × number of inches above 60 inches in height; PBW (kg) for women = 45.5 + 2.3 × number of inches above 60 inches in height.

†Goal peak will depend on severity and location of infection.

‡Dosage interval (hours) should be adjusted based on renal function.

§This can be given as 3 mg/kg once daily in patients with streptococcal endocarditis.

‖In order to apply the Hartford nomogram, doses of 7 mg/kg for gentamicin/tobramycin and 15 mg/kg for amikacin must be used. (See the bibliography for other nomograms for lower doses that are not included here.)

dosing. Peaks should be obtained at steady state, 1 hour after completing the infusion of the fourth or fifth dose. Troughs should be obtained at steady state prior to the fourth or fifth dose. A random level 6 to 14 hours after the first dose should be obtained in patients receiving once-daily or extended interval dosing. This level should be applied to various nomograms that aid in dosing. Figure 17.1 is the most commonly used nomogram, the Hartford nomogram. Patients on the borderline of a dosage interval should be dosed using the greater dosage interval. In patients receiving amikacin, the random level should be divided by 2 before applying the nomogram.

VANCOMYCIN

Vancomycin is a glycopeptide antibiotic that inhibits cell wall synthesis in gram-positive bacteria. It has activity against many gram positives but is primarily used for resistant species, including methicillin resistant *Staphylococcus aureus* (MRSA). Vancomycin is available in both parenteral and enteral dosage forms; however, the oral formulation has poor bioavailability and is only used for *Clostridium difficile* colitis. When given parenterally, vancomycin is rapidly distributed within 30 minutes to 1 hour. Overall, vancomycin has a volume of distribution of 0.4 to 1 L/kg and has variable penetration into body tissues (55% to 40% in lung tissue and 10% in cerebrospinal fluid relative to serum concentrations). Vancomycin is renally eliminated with a prolonged half-life commonly observed in patients with renal insufficiency. In patients with normal renal function, the elimination half-life is 6 to 12 hours.

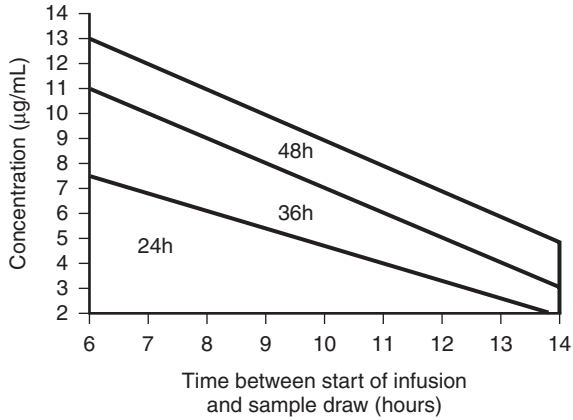


Figure 17.1 The Hartford nomogram for determining the appropriate dosing interval for gentamicin and tobramycin at 7 mg/kg actual body weight.* Instructions for use of nomogram: 1) Draw a blood level of the antibiotic between 6 and 14 hours after the *start* of the initial infusion of 7 mg/kg gentamicin or tobramycin and note the time interval of the blood draw relative to the start of the infusion; 2) Find the point where the concentration of the drug on Y-axis intersects the time interval on X-axis; 3) If the point falls under the lowest slanting line, the dosing interval should be every 24 hours; 4) If the point falls between the lowest and the middle lines, then the interval should be every 36 hours (If every 36-hour dosing interval is not done in a hospital, then the 48-hour interval should be used); 5) If the point falls between the middle and the highest lines, the interval should be every 48 hours; 6) If the point falls *on* a line, the interval should be as if the point fell beneath the line; 7) If the point falls *above* the highest line, the nomogram is not valid and cannot be used to determine dosing interval (see text for alternative dosing method). Note: This nomogram has been validated to achieve an appropriate peak level if the agent is infused over the usual infusion time of 1 to 1.5 hours while allowing the blood level to fall to zero before the next dose. If the level drawn 1 hour prior to the next dose is not zero, then the interval is inappropriate (i.e., too short) and dosing should be done by levels (see text for details). *Use adjusted body weight if actual body weight >120% predicted body weight (see Table 17.1). *Adapted from Nicolau DP, Freeman CD, Belliveau PP, et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother 39(3):650-655, 1995.*

To maximize anti-bacterial activity, total exposure of vancomycin (area under the curve, AUC) in relation to the MIC of the organism should be > 400. In clinical practice, obtaining the multiple serum concentrations necessary to calculate an AUC is difficult. This has led to the clinical use of monitoring trough concentrations as measures of efficacy as they can be used as surrogate markers of AUC. For most indications, with the exception of skin and skin structure (soft tissue) infections, vancomycin trough concentrations of 15 to 20 mg/dL are recommended. Trough concentrations should be obtained at steady state, usually just prior to the fourth or fifth dose of a patient's regimen. In all patients, vancomycin trough concentrations of less than 10 mg/dL should be avoided as this has been correlated to the development of resistance in *S. aureus*. To rapidly achieve this target trough concentration, a loading dose of 25 to 30 mg/kg can be used with subsequent doses of 15 to 20 mg/kg. All doses should be based on actual rather than ideal body weight. Frequency of administration should be adjusted based on a patient's renal function including the use of renal replacement therapy. Patients who receive intermittent hemodialysis with high-flux membranes will commonly need doses of vancomycin after each hemodialysis session, as vancomycin is efficiently removed. Patients receiving continuous renal replacement therapy will often require daily doses of vancomycin as well depending on the rate of blood flow, dialysate flow, and the time the circuit is functioning. In these patients and in all patients, the frequency of trough monitoring should be based on clinical judgment but should occur at least once weekly in stable patients.

Historically, the nephrotoxicity associated with vancomycin has been attributed to the use of an impure product during the first 6 years of its availability. When used as a single agent, the risk of vancomycin-induced nephrotoxicity is less than 5%. Older patients, those with high trough concentrations (greater than 30 mg/dL), those that receive concomitant nephrotoxic agents such as aminoglycosides, and those who receive the drug for an extended period of time are at higher risk for nephrotoxicity.

PHENYTOIN

Phenytoin is an antiepileptic drug that is well absorbed orally (70% to 100%) with decreased absorption when given during enteral feedings. Phenytoin distributes widely throughout the body and is highly protein bound (90% to 95%) to albumin. Decreases in serum albumin or in the affinity for phenytoin to bind to albumin (such as during acidemia) will increase the free fraction (unbound portion) of phenytoin. This increase in unbound phenytoin can lead to phenytoin toxicities. Important disease states that change free phenytoin concentrations are burns, uremia, cystic fibrosis, and jaundice/hyperbilirubinemia. Drug-drug interactions can also change free phenytoin concentrations. Important drug interactions with phenytoin are valproic acid, carbamazepine, voriconazole, warfarin, benzodiazepines, phenobarbital, lithium, and fluconazole. Phenytoin is metabolized by the liver via a saturable enzyme system and very little phenytoin is excreted in the urine.

A common loading dose of phenytoin for status epilepticus is 15 to 20 mg/kg based on total body weight as an intravenous (IV) mini-infusion (Chapter 70). Maintenance doses are 5 to 7 mg/kg/day based on predicted body weight (PBW) for both IV and oral formulations. Target total phenytoin levels should be between 10 to 20 mcg/mL Target free phenytoin levels are 1 to 2 mcg/mL. The half-life of phenytoin is 15 to 22 hours. Because of this longer half-life, phenytoin levels should be monitored 3 to 5 days after dose initiation or dose changes to achieve a steady-state concentration. A 2-hour postload level may be obtained in actively seizing patients to ensure that the patient is within the therapeutic range.

Common adverse reactions for phenytoin include ataxia, nystagmus, dizziness, somnolence, and confusion, all of which are dose related. Thrombophlebitis is also common, and hypotension and bradycardia also occur frequently with rapid IV administration because of the polyethylene glycol diluent present in the solution.

FOSPHENYTOIN

Fosphenytoin is a prodrug of phenytoin that is converted to phenytoin by plasma esterases and is only available as an IV/intramuscular (IM) formulation. Fosphenytoin is 100% absorbed via the IM route, whereas phenytoin should not be administered IM. Phenytoin has a pH of 12 and causes severe skin and tissue necrosis if injected IM. Fosphenytoin is similar to phenytoin in volume of distribution and also is metabolized via the liver. Fosphenytoin is also highly protein bound, and the same populations are at risk for increased unbound fraction and toxicity as with phenytoin. The drug-drug interactions are expected to be the same as those of phenytoin.

Fosphenytoin dosing for status epilepticus is 15 to 20 mg/kg of phenytoin equivalents based on total body weight. The dose, concentration, and infusion of fosphenytoin should always be prescribed in phenytoin equivalents. No conversion or calculation is necessary for dosing, as this is accounted for in the formulation of fosphenytoin. Maintenance doses are also 5 to 7 mg/kg/day based on PBW with target total phenytoin levels of 10 to 20 μg/mL and free phenytoin levels of 1 to 2 μg/mL. Fosphenytoin is monitored in the same manner as phenytoin with levels obtained 3 to 5 days after medication initiation or dose changes.

Adverse reactions of fosphenytoin are similar to phenytoin and include nystagmus, ataxia, dizziness, somnolence, and confusion, all of which are dose related. Fosphenytoin may be administered more rapidly than phenytoin at a rate of 150 mg/min compared to a maximal rate of 50 mg/min for phenytoin. Less hypotension and bradycardia are associated with the use of fosphenytoin because fosphenytoin does not contain polyethylene glycol as a drug diluent. Thrombophlebitis is also much less common given its lower pH of 8.8 compared to that of phenytoin (pH = 12). Although no formal criteria exist for the use of fosphenytoin, some literature suggest it is the preferred agent in patients < 7 or > 60 years of age and in those who have a history of underlying cardiovascular disease, chronic or acute debilitating illness, emaciation, hyponatremia, peripheral vascular disease, hemodynamic instability, sepsis, or poor intravenous access (e.g., smaller than a 20 gauge IV).

DIGOXIN

Digoxin is a cardiac glycoside that inhibits the Na/K ATP-ase pump in myocardial cells. This inhibition results in a positive inotropic effect. Digoxin also results in an increase in vagal tone, thus decreasing sympathetic output from the central nervous system, and a decrease in the rate of atrioventricular nodal conduction. The first mechanism is primarily responsible for the use of digoxin in patients with heart failure, whereas the second mechanism results in a decreased heart rate in patients with atrial fibrillation. Absorption of oral digoxin is nearly complete (60% to 100%) depending on dosage form and occurs in 1 to 3 hours. The distribution phase is prolonged (6 to 12 hours), resulting in a delay of its therapeutic effects. Digoxin has a large volume of distribution (7.3 L/kg based on ideal body weight), which can be altered by certain patient-related factors. Patients with hypothyroidism, impaired renal function, and the elderly have decreased volumes of distribution, whereas those with hyperthyroidism have increased volumes of distribution. Digoxin metabolism and elimination are also dependent on certain factors, but in patients with normal renal function, it is 75% renally eliminated with 25% hepatic metabolism. In patients with severe heart failure in which hepatic blood flow is compromised, nonrenal clearance is decreased, thus renal function is extremely important is determining dosing of digoxin.

Because of the long half-life and volume of distribution, patients who need digoxin should receive a loading dose. This loading dose should be based on ideal body weight and will vary in patients with renal dysfunction. Eighteen to 24 hours after a loading dose, a digoxin serum concentration should be obtained. Serum concentrations vary based on clinical indication with a goal of 0.5 to 0.9 ng/mL in patients with heart failure and less than 2 ng/mL in patients with atrial fibrillation. Serum drug concentrations greater than 1 ng/mL in patients with heart failure have

TABLE 17.2 ■ **Recommended Dosing of Digoxin Based on Renal Function**

Loading Dose	Maintenance Dose	Desired Serum Concentration	Timing of Serum Concentrations
Normal Renal Function			
1 mg dosed as 0.5 mg once, then 0.25 mg every 4–6 hours for 2 doses	0.125 mg–0.25 mg	Heart failure: 0.5–0.9 ng/mL Atrial fibrillation: <2 ng/mL	18–24 hours post loading dose
Decreased Renal Function			
0.75 mg, dosed as 0.5 mg, then 0.125 mg every 4–6 hours for 2 doses	0.125 mg every 24-48 hours	Heart failure: 0.5–0.9 ng/mL Atrial fibrillation: <2 ng/mL	18–24 hours post loading dose

been associated with an increased risk for mortality, particularly in women. Patients using digoxin for atrial fibrillation should be titrated to rate control as long as serum drug concentrations do not exceed 2 ng/mL, because levels greater than 2 ng/mL have been associated with increased toxicities. Table 17.2 contains both loading and maintenance dosing strategies for digoxin in patients with either heart failure or atrial fibrillation.

Unfortunately, digoxin toxicity can occur at any serum drug concentration and should be diagnosed based on clinical signs and symptoms such as cardiac dysrhythmias, atrioventricular block, bradycardia, severe hyperkalemia, and nausea and vomiting. Toxicity should subsequently be correlated with serum drug concentrations. Patients with renal dysfunction, hypokalemia, hypothyroidism, advanced age, and increased digoxin concentrations are at greater risk for developing toxicities. Also patients receiving verapamil, amiodarone, or quinidine, which increase the serum drug concentrations of digoxin, should be monitored carefully. Because of the large volume of distribution, digoxin is not easily dialyzable and should severe toxicity occur, digoxin-immune Fab (Digibind) should be given. The dosage of digoxin-immune Fab is based on the total amount of digoxin ingested and whether the ingestion is chronic or acute.

UNFRACTIONATED HEPARIN

The anticoagulant unfractionated heparin (UFH) potentiates the binding of antithrombin III to thrombin (factor II) and factor X, preventing these coagulation factors from activating fibrinogen to fibrin. UFH is absorbed erratically from the subcutaneous (SQ) route with potentially decreased absorption in the obese and those with decreased perfusion to the subcutaneous tissues such as shock. The distribution of UFH is limited to the intravascular space almost exclusively. The major metabolism of UFH is via the reticuloendothelial system. The elimination half-life of UFH is 1 to 2 hours and is prolonged in obese patients with hepatic dysfunction and malignancy.

UFH may be given either SQ or IV. The SQ route is almost exclusively reserved for the administration of prophylactic doses of UFH, typically 5000 units every 8 to 12 hours. The dose of UFH for deep venous thromboembolism (DVT) prophylaxis depends on the patient's thromboembolism risk and patient factors such as weight and body mass index. Two common uses of heparin IV are for the treatment of DVT/pulmonary embolism (PE) and the treatment of acute coronary syndrome (ACS). The dosage of heparin for the treatment of DVT/PE is based on total body weight and is 80 units/kg IV bolus followed by an 18 units/kg/hour continuous IV infusion (Chapter 77).

It is important to note that the dose of UFH for the treatment of ACS is different than the dose for DVT/PE. The bolus dose is 60 to 70 units/kg IV dosed on total body weight (up to

a maximum of 5000 units), followed by a continuous IV infusion of 12 to 15 units/kg/hour (up to a maximum of 1000 units/hour).

Heparin is monitored for efficacy and safety using activated partial thromboplastin time (aPTT) measurements every 6 hours after initiating a continuous infusion. The target aPTT measurements for the treatment of DVT/PE are 0.3 to 0.7 IU/mL of anti-Xa activity based on the institution specific reagent. The target aPTT measurement for the treatment of ACS is 50 to 70 seconds, also based on the institution specific reagent. There is not one universal dosing protocol for UFH promoted by the American College of Chest Physicians Guidelines because each institution must set the target aPTT range based on the particular reagent it uses to measure the aPTT. Many institutions have chosen to develop institution-specific protocols for both DVT/PE and ACS in order to minimize dosing errors and decrease the time to achieve a therapeutic aPTT.

Important adverse reactions to heparin include bleeding, both major and minor, and thrombocytopenia. The thrombocytopenia associated with heparin can be one of two types (Chapter 45). The first type is heparin-immune mediated thrombocytopenia (HIT) in which all forms of heparin must be discontinued immediately and the patient should not be exposed to heparin again without the risk of forming either a limb- or life-threatening thromboembolism. The second type is heparin-associated thrombocytopenia in which the patient may receive heparin again in the future but will likely experience thrombocytopenia again.

LOW-MOLECULAR-WEIGHT HEPARIN

Low-molecular-weight heparins (LMWHs) are anticoagulants with molecular weights of 4000 to 6000 Daltons that, like UFH, also potentiate the binding of antithrombin III to factor X. LMWHs are > 90% to 99% absorbed when administered via the SQ route and distribute mostly to the intravascular space. Patients with anasarca or decreased perfusion to the subcutaneous or epidermal skin layers may have erratic or unpredictable absorption of LMWH products. LMWHs are metabolized via the liver into lower-molecular-weight fragments with little anticoagulant activity. The elimination half-life of LMWHs is approximately 4.5 to 6 hours and much of LMWHs are eliminated in the urine (40%).

The LMWH enoxaparin (Lovenox) is administered SQ for the treatment of DVT/PE or ACS at a dose of either 1 mg/kg SQ every 12 hours or 1.5 mg/kg SQ daily based on total body weight. Enoxaparin may also be given as DVT prophylaxis at a dose of either 40 mg SQ daily or 30 mg every 12 hours depending on the patient's risk factors for a DVT. Dalteparin (Fragmin), another LMWH, may be given for treatment of DVT/PE at a dose of 200 IU/kg SQ daily. The treatment dose of dalteparin for ACS is 120 IU/kg SQ every 12 hours (not to exceed 10,000 units every 12 hours). Dalteparin can also be administered as DVT prophylaxis at a dose of 5000 units SQ daily. One advantage of LMWH over UFH is a predictable dose-response relationship in standard dosing ranges up to a weight of 150 kg and a CrCl >30 mL/min. Caution should be used in administering LMWHs to patients with weights > 150 kg or with a CrCl < 30 mL/min. These populations will require monitoring to ensure supratherapeutic levels of anticoagulation are not achieved with standard dosing. LMWHs are monitored using anti-Xa levels with target therapeutic levels of 0.6 to 1 IU/mL.

The adverse events of LMWHs and UFH are similar: bleeding and thrombocytopenia. The risk of HIT is decreased compared to UFH (<1% versus 1% to 3%), but in the event a patient has HIT to UFH, a LMWH product cannot be used as an alternative.

DIRECT THROMBIN INHIBITORS

Argatroban, bivalirudin, and lepirudin are the three most commonly used direct thrombin inhibitors (DTIs). DTIs are anticoagulants that reversibly bind to thrombin, thus inhibiting fibrin

formation. Although the mechanism of action is the same for each DTI, the pharmacokinetics of each drug is distinct.

Argatroban is administered only IV for the treatment or prevention of HIT, and its distribution is not limited to the intravascular space. Argatroban is bound to two major proteins: albumin (20%) and p-glycoprotein (35%). Argatroban is metabolized in the liver via hydroxylation and aromatization to four metabolites, three of which are inactive. The only active metabolite, M1, is three- to fivefold weaker in potency compared to the parent argatroban compound. Argatroban is eliminated in 39 to 51 minutes, but this time prolongs significantly in the presence of hepatic impairment to up to 181 minutes. Most of argatroban and its metabolites are excreted in the feces (65%) and the urine (22%). There is also evidence to suggest that patients with hypoperfusion to the liver such as patients with multisystem organ failure, heart failure, severe anasarca, or after cardiac surgery should receive reduced-dose argatroban because of decreased metabolism and clearance.

Argatroban is dosed at 2 mcg/kg/min for the treatment or prevention of HIT. This dose is reduced to 0.5 mcg/kg/min in patients with hepatic impairment. The dose of argatroban should also be reduced in the hypoperfused population previously described with a starting dose of 0.5 mcg/kg/min to 1.2 mcg/kg/min.

Lepirudin as a continuous IV infusion has been approved by the U.S. Food and Drug Administration (FDA) for the prevention of HIT, but it is also used off label for the treatment of HIT. Lepirudin may also be given as a SQ injection, where it is 100% absorbed. This route has been used for DVT prophylaxis in HIT-positive patients, although there are limited data to support this use. Lepirudin distributes well beyond the intravascular space, and much of the drug is confined to extracellular fluids. Lepirudin is metabolized via hydrolysis and is excreted in 1.3 hours. This time is markedly prolonged in renal impairment as 48% of lepirudin is excreted in the urine, mostly as unchanged drug. The time to excrete lepirudin in severe renal impairment can be as long as 2 days.

Lepirudin is administered as an IV infusion at a dose of 0.10 mg/kg/hour for the prevention or treatment of HIT. A bolus dose of lepirudin 0.2 to 0.4 mg/kg may be given but only when a patient has either a limb- or life-threatening thrombosis.

Similar to lepirudin, *bivalirudin* is typically administered via continuous IV infusion but may be administered via the SQ route; however, it is only 40% absorbed from this route. Bivalirudin distributes mostly to the intravascular compartment and is metabolized via proteases in the blood. Bivalirudin is eliminated in 25 minutes, but this time is prolonged in renal impairment up to 3.5 hours for dialysis-dependent patients because a small portion (20%) of bivalirudin is excreted via the kidneys.

The dose of bivalirudin for treatment or prevention of HIT is 0.15 to 0.20 mg/kg/hour as a continuous IV infusion. There are limited data to support the use of bivalirudin for the treatment or prevention for HIT alone. The majority of the data for the use of bivalirudin focuses on patients undergoing percutaneous coronary intervention (PCI) or percutaneous transluminal coronary angioplasty, with or without risk of HIT.

Each of these agents are monitored using aPTT measurements with target argatroban aPTT 1.5 to 2.5 times the baseline aPTT, lepirudin 1.5 to 2 times the baseline aPTT, and bivalirudin 1.5 to 2.5 times the baseline aPTT. For all agents, the aPTT should not exceed 100 seconds. Notably, argatroban is the only DTI that increases INR, but this increase is a false elevation because of an interaction between argatroban and the INR assay.

The important adverse events are similar for all agents and include bleeding, both major and minor. Importantly, up to 40% of patients who receive lepirudin will develop antibodies to the drug and upon reexposure may experience anaphylaxis. Based on these data, once a patient has one treatment exposure with lepirudin, it is recommended to avoid administering lepirudin to that patient again. It is not believed that antibodies develop to either argatroban or bivalirudin.

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CHAPTER 18

Rational Use of Antimicrobials

Kara B. Mascitti ■ Neil Fishman

Antibiotic use in the intensive care unit (ICU) has been impacted by two major trends. First, although the number of antibiotics available for use in the ICU setting rose dramatically through the 1980s, the number of new antimicrobial agents approved by the Food and Drug Administration (FDA) has decreased by 80% since the 1990s. Second, many pathogens infecting ICU patients have become increasingly resistant to both older and newer antimicrobial agents, often the result of starting or continuing antibiotics that are inappropriate for the clinical situation. As a result, there has been an effective decline in the number of antibiotics available for use in the ICU, which some have labeled as a return to the preantibiotic era. This emphasizes the importance of a rational approach to both empirical and directed use of antibiotics in the ICU.

Empirical Antimicrobial Therapy

Rational initiation of empirical antibiotic therapy requires an understanding of the complexities involved in the diagnosis of infection in the ICU setting. First, ICU patients with underlying infection often may not exhibit the usual signs and symptoms of infection like fever, or leukocytosis. Likewise, even when these classic signs are present (Chapter 13), they can be problematic because none of them alone, or even in combination, is highly predictive of an underlying infection.

FEVER AND LEUKOCYTOSIS

Fever is defined as an elevated core body temperature albeit with no consensus as to the specific threshold temperature that qualifies as a fever. For example, the Centers for Disease Control and Prevention (CDC) uses > 100° F for a fever in its case definition of influenza and > 101° F (> 38.0° C) for the purposes of surveillance for health care–associated infections (HAIs) (nosocomial infections). Fever is caused by the release of cytokines (so-called endogenous pyrogens, e.g., IL1) in response to injury, inflammation, antigenic challenge, or infection. Thus, fever itself cannot reliably distinguish infectious from noninfectious causes. Despite its seemingly common occurrence, few prospective data exist on the frequency and causes of fever specifically in ICU patients. A small prospective study in adult ICU patients published in 1999 showed that fever occurred in 70% of ICU admissions but was associated with infection in only 53% of cases, confirming that fever is not a specific marker for infection. Furthermore, fever has been found to be present in only half the cases of sepsis and postoperative infections, indicating that it is also not a sensitive marker for infection in these populations.

In non-ICU studies, many hospitalized patients with fever but no clinical evidence for infection received antibiotics, suggesting that much of the antibiotic use in non-ICU patients that is initiated for fevers alone is unnecessary and can be eliminated without jeopardizing patient care. By inference, starting antibiotics for fever *alone* in ICU patients is inappropriate (with the exception of patients with neutropenia [see Chapter 24]), and the presence of fever should instead stimulate a systematic search for its cause (see Chapters 13 and 14).

Like fever, leukocytosis (elevated white blood cell [WBC] count, specifically WBC > 15,000 cells/μL) also has a low specificity. Although such a degree of leukocytosis is associated with an increased risk of bacterial infection, almost half of such patients have no identifiable infection.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS), SEPSIS, AND SEPTIC SHOCK

The *systemic inflammatory response syndrome* (SIRS) is defined as the simultaneous presence of two or more physiologic signs that can result from systemic inflammation: (1) fever (or hypothermia), (2) tachycardia, (3) tachypnea, and (4) a neutrophilic leukocytosis. SIRS can arise from infectious or noninfectious causes. *Sepsis* has been defined as SIRS with clinical evidence (or high suspicion) of infection. *Severe sepsis* refers to the clinical situation of sepsis with evidence of (otherwise unexplained) inadequate end organ perfusion. *Septic shock* is severe sepsis with clinically significant hypotension (see Chapter 10). Even though infection is common in patients with severe sepsis (present in ~90% of patients in one large prospective epidemiologic study), bloodstream infection (bacteremia or fungemia) was documented in only about one quarter of this group of patients overall.

Despite the above-mentioned limitations of using fever, leukocytosis, and SIRS/sepsis as markers of infections, these signs are still clinically important and their presence should always prompt a thorough search for their cause (see Chapters 10, 13, and 14).

An additional complexity of diagnosing infection in ICU patients is that even objective clinical data, such as microbiologic cultures, can often be confusing. For example, a positive culture of sputum or a tracheal aspirate for a pathogenic organism does not necessarily prove the presence of a health care–associated pneumonia or even tracheobronchitis. Likewise, a negative culture—for example, a tracheal aspirate sent the day after the start of new antimicrobials—does not confirm the absence of infection. Finally, some culture results may be uninterpretable because of an ill-considered approach to the diagnostic evaluation, such as relying exclusively on blood cultures obtained from existing central venous catheters without the benefit of cultures drawn from a peripheral site. This can complicate the interpretation of cultures growing common skin contaminants such as coagulase-negative *Staphylococcus* species (see Chapter 14).

A final consideration when selecting an appropriate empirical antibiotic regimen is an appreciation of the epidemiology of common health care–associated infections within one's own ICU and hospital. Rates of health care–associated infections among ICU admissions range from 3% to 31% and can vary between community and university hospitals as well as between different types of ICUs within the same hospital. Likewise, the prevalence of specific pathogens and their antimicrobial resistance patterns can vary considerably among different hospitals, ICU types, and even over time within the same ICU. Understanding one's local epidemiology is crucial for selecting a regimen that provides adequate antimicrobial coverage for the most likely infecting pathogens while also minimizing the risk of promoting antimicrobial resistance with agents that have too broad a spectrum of coverage.

Antibiotic Stewardship in the ICU

Antimicrobial stewardship is a rational, systematic approach to the use of antimicrobial agents that involves selecting an appropriate drug and optimizing its dose and duration in order to cure an infection, while minimizing toxicity and conditions for selection of resistant bacterial strains. The most common errors in antibiotic use in the ICU are both in the incorrect initial choice of empirical agents as well as in the failure to narrow antimicrobial coverage and limit antibiotic duration once the results of cultures and diagnostic studies become available.

Since the early 2000s, there has been a significant rise in the prevalence of multidrug-resistant organisms, especially among infections found in the ICU. More than half of *Staphylococcus aureus*

isolates in ICUs are methicillin resistant, and resistance of certain gram-negative organisms to third-generation cephalosporins, fluoroquinolones, and carbapenems can be as high as 20% to 30%. Failure to select an empirical antimicrobial regimen for critically ill patients that covers such pathogens when present can have serious implications, as inadequate initial antibiotic therapy is associated with worse clinical outcomes. Choice of specific empirical agents should thus be guided by antibiotic resistance patterns in one's own community and hospital.

By the same token, limiting the spectrum and duration of antimicrobials when appropriate is equally, if not more, important. Often overlooked or minimized, the complications of antimicrobial use are important to consider at both the individual and community levels. Toxicities, such as renal failure, *Clostridium difficile* infection, drug fever, and serious allergic reactions, are associated with increased morbidity and mortality and lead to further diagnostic studies as well as additional hospitalization days and increased costs of care. Furthermore, ICU patients given broad-spectrum antibiotics are predisposed to colonization and eventual infection with resistant organisms such as methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococcus (VREC), vancomycin-intermediate *S. aureus,* extended-spectrum beta-lactamase–producing (ESBL+) Enterobacteriaceae, carbapenemase-producing Enterobacteriaceae, and multidrug-resistant *Acinetobacter baumannii*. Exposure to broad-spectrum antibiotics is also a known risk factor for the development of invasive fungal infections. Infections with any of these resistant organisms or fungi lead to poor clinical outcomes for the patients as well as negative institutional and economic outcomes.

Antimicrobial Agents

Obviously, one cannot make rational antibiotic choices without a better understanding of the agents themselves. This includes their mechanisms of action, spectra of activity, common adverse effects, and costs (Tables 18.1 to 18.4). Proper dosage adjustments must be made for renal or hepatic insufficiency as well as other situations known to alter pharmacokinetics (see Chapter 17).

Common Health Care–Associated Infections in the ICU

Several types of infections are particularly common among ICU patients (see also Chapter 14). Specific considerations for the diagnosis of these infections are discussed here, and suggested empirical antibiotic regimens for each infection type are listed in Table 18.5. For all infection types, initial empirical antibiotic regimens should be reevaluated after 48 to 72 hours, and the choice of agent(s) to be continued should be tailored based on available culture and susceptibility data.

HEALTH CARE–ASSOCIATED PNEUMONIAS

Health care–associated pneumonias are common in the ICU, especially in patients receiving mechanical ventilation, with a mortality of 30% to 70%. Although survival rates improve with appropriate treatment, pneumonia in the ICU patient can be particularly difficult to diagnose. Findings of new or progressing pulmonary infiltrates associated with fever, leukocytosis, and purulent tracheal secretions are neither sensitive nor specific. Radiographic changes mimicking pneumonia may be caused by many noninfectious causes, including atelectasis, atypical pulmonary edema, acute respiratory distress syndrome (ARDS), hemorrhage, or chemical pneumonitis. Tracheal cultures can grow organisms because of colonization of proximal airways, making it difficult to distinguish between colonizers and true pathogens and leading to treatment on the basis of false-positive results. Quantitative cultures of distal pulmonary regions have reasonable specificity and sensitivity *before* administration of new antibiotics but, when obtained after antibiotic

TABLE 18.1 ■ **Penicillins: General Antibacterial Spectrum and Side Effects**

Antibiotic Group (Examples)	Covers	Does Not Cover	Potential Side Effects and Comments
Natural penicillins (penicillin G, penicillin V)	Most *Streptococcus* spp. Some enterococci Gram-positive anaerobes	Up to 35% of *Streptococcus pneumoniae* may be resistant *Staphylococcus* spp. Most enterococci Gram-negative aerobes Gram-negative anaerobes	Hypersensitivity reactions, interstitial nephritis, neutropenia High doses prevent platelet aggregation and increase bleeding times
Aminopenicillins (ampicillin, amoxicillin)	Most *Streptococcus* spp. Some enterococci Gram-positive anaerobes Some *Escherichia coli* Some *Proteus* spp. *Listeria monocytogenes*	Some *S. pneumoniae* *Staphylococcal* spp. Some enterococci Most gram-negative aerobes Gram-negative anaerobes	See "Natural penicillins" above Ampicillin is agent of choice for *Listeria* infections
Penicillinase-resistant penicillins (methicillin, nafcillin, dicloxacillin, oxacillin)	All *Streptococcus* spp. and methicillin-sensitive *Staphylococcus aureus* (MSSA)	*Enterococcus* spp. Methicillin-resistant *S. aureus* (MRSA) Coagulase-negative *Staphylococcus* spp. Gram-negative aerobes Anaerobes	See "Natural penicillins" above
Semisynthetic penicillins (piperacillin)	*Streptococcus* spp. Some enterococci Most gram-negative aerobes *Pseudomonas aeruginosa* Most anaerobes	*Staphylococcus* spp. Some enterococci Some gram-negative aerobes *B. fragilis*	See "Natural penicillins" above *Usual* doses prevent platelet aggregation and increase bleeding times
Penicillins with β-lactamase inhibitors (ampicillin-sulbactam, amoxicillin-clavulanate, ticarcillin-clavulanate, piperacillin-tazobactam)	*Streptococcus* spp. Some enterococci (except ticarcillin-clavulanate) MSSA Most gram-negative aerobes *P. aeruginosa* (ticarcillin-clavulanate and piperacillin-tazobactam) Anaerobes including *Bacteroides fragilis*	Some enterococci MRSA Coagulase-negative *Staphylococcus* spp. No pseudomonal coverage for ampicillin-containing agents	See "Natural penicillins" above

From Hospital Infection Control Practices Advisory Committee (HICPAC): Recommendations for preventing the spread of vancomycin resistance. MMWR Morb Mortal Wkly Rep 44(RR12):1-13, 1995.

administration, exhibit a marked loss of sensitivity, leading to false-negative results (see Chapter 14). Guidelines suggest limiting antibiotic therapy to 7 or 8 days in patients with uncomplicated cases who have a good clinical response and no evidence of infection with nonfermenting gram-negative bacilli (e.g., *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, *Delftia acidovorans*, and *Burkholderia cepacia*).

Text continued on page 189

TABLE 18.2 ■ **Cephalosporins: General Antibacterial Spectrum and Side Effects**

Antibiotic Group (Examples)	Covers	Does Not Cover	Potential Side Effects and Comments
First-generation cephalosporins (cefazolin, cephalexin, cefadroxil)	*Streptococcus* spp. Methicillin-sensitive *Staphylococcus aureus* (MSSA) Some *Escherichia coli* Some *Proteus mirabilis*	*Enterococcus* spp. Methicillin-resistant *S. aureus* (MRSA) Coagulase-negative *Staphylococcus* spp. *Haemophilus influenzae* Most gram-negative aerobes *Pseudomonas aeruginosa* Anaerobes	Hypersensitivity reactions Interstitial nephritis 5%–10% cross-reactivity between cephalosporins and penicillins in penicillin-allergic patients (see Chapter 32)
Second-generation cephalosporins (cefuroxime, cefotetan, cefoxitin)	*Streptococcus* spp. MSSA (not the preferred agent) Many gram-negative aerobes *H. influenzae*	*Enterococcus* spp. MRSA Coagulase-negative *Staphylococcus* spp. *Enterobacter* spp. *P. aeruginosa* Anaerobes	See "First-generation cephalosporins" above
Third-generation cephalosporins (ceftriaxone, cefotaxime, cefixime, ceftazidime)	*Streptococcus* spp. MSSA (*only* ceftriaxone, not the preferred agent) Most gram-negative aerobes *P. aeruginosa* (*only* for ceftazidime) Some anaerobes	*Enterococcus* spp. MRSA Coagulase-negative *Staphylococcus* spp. Extended-spectrum beta-lactamase producing (ESBL+) gram-negative aerobes *Bacteroides fragilis*	See "First-generation cephalosporins" above Biliary sludge formation associated with ceftriaxone
Fourth-generation cephalosporins (cefepime)	*Streptococcus* spp. Most gram-negative aerobes *P. aeruginosa* Some anaerobes	*Enterococcus* spp. *S. aureus* Coagulase-negative *Staphylococcus* spp. ESBL+ gram-negative aerobes *B. fragilis*	See "First-generation cephalosporins" above
Fifth-generation cephalosporin (ceftaroline)	*Streptococcus* spp. *Staphylococcus* spp. (including MRSA) Most gram-negative aerobes Some anaerobes	*Enterococcus* spp. *P. aeruginosa* ESBL+ gram-negative aerobes *B. fragilis*	See "First-generation cephalosporins" above

From Hospital Infection Control Practices Advisory Committee (HICPAC): Recommendations for preventing the spread of vancomycin resistance. MMWR Morb Mortal Wkly Rep 44(RR12):1-13, 1995.

TABLE 18.3 ■ **Nonpenicillin and Noncephalosporin Antibiotics: General Antibacterial Spectrum and Side Effects**

Antibiotic Group (Examples)	Covers	Does Not Cover	Potential Side Effects and Comments
Aminoglycosides (amikacin, gentamicin, streptomycin, tobramycin)	Used for synergy (gentamicin) against *Streptococcus* spp., *Staphylococcus aureus*, and *Enterococcus* spp. Most gram-negative aerobes Some *Pseudomonas aeruginosa* Gram-negative anaerobes	Some coagulase-negative *Staphylococcus* spp. Anaerobes	Nephrotoxicity, ototoxicity, neuromuscular blockade Doses need to be individually calculated, and serum levels and renal function should be monitored (see Chapter 17) Once-daily dosing decreases nephrotoxicity
Monobactams (aztreonam)	Most gram-negative aerobes Most *P. aeruginosa*	Gram-positive aerobes Extended-spectrum beta-lactamase producing (ESBL+) gram-negative aerobes Anaerobes	Safe for use in penicillin-allergic patients; does not provide the synergy of aminoglycosides when used in combination with cell wall–active agents
Carbapenems (doripenem, ertapenem, imipenem, meropenem)	*Streptococcus* spp. MSSA *Enterococcus* spp. Most gram-negative aerobes (including ESBL+) *P. aeruginosa* (except ertapenem) Anaerobes including *Bacteroides fragilis*	MRSA Coagulase-negative staphylococci may be resistant Carbapenemase producing (KPC+) gram-negative aerobes	Seizures may occur, particularly in patients with underlying CNS pathology or renal insufficiency (mostly with imipenem); hypersensitivity, cross-reactivity between penicillin and carbapenems occurs (50%) (see Chapter 32)
Chloramphenicol	*Streptococcus* spp. Some *Staphylococcus* spp. Most gram-negative aerobes Anaerobes	Some *Staphylococcus* spp. *P. aeruginosa*	Dose-related, reversible bone marrow suppression; idiosyncratic dose-independent, generally fatal aplastic anemia (~1/30,000 patients who receive the drug); hemolysis in severe G6PD deficiency; its use should be restricted to clearly defined circumstances owing to its toxicity; effective second-line agent for bacterial meningitis in penicillin-allergic patients
Colistimethate (colistin)	Most gram-negative aerobes (including ESBL+ and KPC+) *P. aeruginosa* *Acinetobacter* spp.	*Streptococcus* spp. *Staphylococcus* spp. *Enterococcus* spp. Some gram-negative aerobes *B. fragilis*	Nephrotoxicity, neurotoxicity, phlebitis at the infusion site

TABLE 18.3 ■ **Nonpenicillin and Noncephalosporin Antibiotics: General Antibacterial Spectrum and Side Effects** (Continued)

Antibiotic Group (Examples)	Covers	Does Not Cover	Potential Side Effects and Comments
Clindamycin	*Streptococcus* spp. MSSA Most MRSA Most anaerobes	*Enterococcus* spp. Some MRSA Coagulase-negative staphylococci Gram-negative aerobes *P. aeruginosa* *B. fragilis*	Hypersensitivity; increased risk for *Clostridium difficile* colitis
Daptomycin	*Streptococcus* spp. *Staphylococcus* spp. *Enterococcus* spp.	Gram-negative aerobes All anaerobes	Myopathy, especially at higher doses or when co-administered with statins
Linezolid	*Streptococcus* spp. *Staphylococcus* spp. *Enterococcus* spp. Gram-positive anaerobes	Gram-negative aerobes Gram-negative anaerobes	Reversible myelosuppression, lactic acidosis, peripheral neuropathy, and optic neuritis (especially with prolonged administration); serotonin syndrome when co-administered with monoamine oxidase inhibitors
Macrolides (erythromycin, clarithromycin, azithromycin)	Most *Streptococcus* spp. *Mycoplasma pneumoniae* Some MSSA *Haemophilus influenzae* and *Moraxella catarrhalis* (*only* azithromycin and clarithromycin) Some anaerobes *Legionella* spp. Second-line agent for *Chlamydia* spp.	Many (18%–33%) *S. pneumoniae* are resistant Most MSSA MRSA Most gram-negative aerobes *P. aeruginosa* *B. fragilis*	GI symptoms (nausea, vomiting, diarrhea) particularly with erythromycin; thrombophlebitis with IV use; interference with hepatic metabolism of other drugs (theophylline, warfarin) Avoid use with HMG-CoA reductase inhibitors ("statins") (may cause rhabdomyolysis)
Metronidazole	Gram-negative anaerobes including *B. fragilis* *Clostridium difficile*	Everything else	Disulfram-like reactions with alcohol ingestion; GI irritation
Quinolones (ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, ofloxacin)	*Streptococcus* spp. (except ciprofloxacin, ofloxacin) *S. aureus* (but resistance may develop quickly) Some enterococci (but resistance may develop quickly) Some gram-negative aerobes Some *P. aeruginosa* *Legionella* spp.	Coagulase-negative *Staphylococcus* spp. Some enterococci Some gram-negative aerobes Some *P. aeruginosa* Anaerobes (except for moxifloxacin)	Mild GI symptoms; mild CNS symptoms (headache, dizziness); rash; avoid in pregnant or nursing mothers and children because of possible cartilage toxicity in infants or children; oral bioavailability similar to IV

TABLE 18.3 ■ **Nonpenicillin and Noncephalosporin Antibiotics: General Antibacterial Spectrum and Side Effects** (Continued)

Antibiotic Group (Examples)	Covers	Does Not Cover	Potential Side Effects and Comments
Quinupristin-dalfopristin	*Streptococcus* spp. *Staphylococcus* spp. *Enterococcus* spp.	Gram-negative aerobes All anaerobes	Venous irritation when administered peripherally; asymptomatic hyperbilirubinemia; arthralgias; some drug-drug interactions
Tetracyclines (tetracycline, doxycycline, tigecycline)	Some *Streptococcus* spp. Some *S. aureus* Some enterococci (VREC) Some gram-negative aerobes (tetracycline and doxycycline) Most gram-negative aerobes including ESBL+ and KPC+ (tigecycline only) Some anaerobes Useful for chlamydial and rickettsial infections	Some *Streptococcus* spp. Some *S. aureus* Most enterococci Some gram-negative aerobes *P. aeruginosa* Some anaerobes including *B. fragilis*	Hypersensitivity; photosensitivity; gray discoloration of teeth in children (do not give to pregnant women or children < 8 y); GI irritation; increases catabolism and blood urea nitrogen
Trimethoprim/sulfamethoxazole	Some *Streptococcus* spp. MSSA and some MRSA Some gram-negative aerobes First-line agent for treatment of *Pneumocystis jiroveci* and *Nocardia* *Listeria* infections in penicillin-allergic patients	Many *S. pneumoniae* (40%) are resistant Groups A and B streptococci always resistant *Enterococcus* spp. Many gram-negative aerobes *P. aeruginosa* Anaerobes	Hypersensitivity (rarely Stevens-Johnson syndrome); GI irritation; bone marrow suppression, particularly in ESRD; displacement of warfarin from albumin binding sites; aseptic meningitis
Vancomycin	*Streptococcus* spp. *Staphylococcus* spp. *Enterococcus* spp. Gram-positive anaerobes Oral vancomycin not absorbed but useful in treatment of *C. difficile* colitis	VREC Gram-negative aerobes *P. aeruginosa* Gram-negative anaerobes	Histamine-related flushing of face, neck, and thorax ("red man syndrome"), which may be ameliorated by slowing infusion of drug to > 1 h; hypersensitivity; neutropenia and thrombocytopenia; 8th cranial nerve toxicity

Abbreviations: CNS, central nervous system; ESBL+, extended-spectrum beta-lactamase producing; ESRD, end-stage renal disease; GI, gastrointestinal; IV, intravenous; MRSA, methicillin-resistant *S. aureus;* MSSA, methicillin-sensitive *S. aureus;* VREC, vancomycin-resistant enterococcus.

TABLE 18.4 ■ **Antifungal Agents: General Antifungal Spectrum and Side Effects**

Antifungal Group (Examples)	Covers	Does Not Cover	Potential Side Effects and Comments
Triazoles (fluconazole)	*Candida albicans* Most nonalbicans *Candida* spp. *Cryptococcus* spp.	*Aspergillus* spp. Some nonalbicans *Candida* spp. *Fusarium* spp. Zygomycetes	Hepatotoxicity; important drug-drug interactions; oral bioavailability similar to IV
Extended-spectrum triazoles (posaconazole, voriconazole)	*Aspergillus* spp. *Candida* spp. *Cryptococcus* spp. *Fusarium* spp. Zygomycetes (posaconazole only)	Zygomycetes (voriconazole)	See "Triazoles" above Also, transient visual disturbance (voriconazole only)
Echinocandins (anidulafungin, caspofungin, micafungin)	*Candida* spp. *Aspergillus* spp.	*Cryptococcus* spp. *Fusarium* spp. Zygomycetes	Generally nontoxic and well tolerated except for nausea, vomiting Few drug-drug interactions
Polyenes (amphotericin, various formulations)	*Aspergillus* spp. *Candida* spp. *Cryptococcus* spp. *Fusarium* spp. Zygomycetes		Nonlipid formulations: fevers and rigors, which may be relieved with premedication with antihistamine and antipyretics; nephrotoxicity, which may be prevented by pre- and postinfusion hydration Lipid-based formulations: same as nonlipid formulations, but less severe

TABLE 18.5 ■ **Antibiotics and Their Daily Costs* for Common Health Care–Associated Infections in the ICU**

Infection	Clinical Situation	Empirical Therapy	Common Organisms
Pneumonia	Cases *without* risk factors for *Pseudomonas aeruginosa* or multidrug-resistant (MDR) pathogens (risk factors include prior ICU, hospital, or long-term care facility stay, steroids or other immunosuppressants, recent antibiotic exposure, high frequency of resistance in the community or hospital unit)	Ampicillin/sulbactam ($20–$40) *or* ceftriaxone ($5–$10) *or* levofloxacin ($40–$60)	Oral flora Enterobacteriaceae MSSA MRSA
	If *P. aeruginosa* or MDR pathogen suspected (see risk factors, above)	[Cefepime ($40–$60) *or* ceftazidime ($30–$60) *or* piperacillin/tazobactam ($80–$100)] ± [amikacin ($5–$10) *or* tobramycin ($15–$20)]	*Pseudomonas* *Acinetobacter baumannii* MDR gram-negative aerobes

TABLE 18.5 ■ **Antibiotics and Their Daily Costs* for Common Health Care–Associated Infections in the ICU** (Continued)

Infection	Clinical Situation	Empirical Therapy	Common Organisms
	If high local prevalence of extended-spectrum beta-lactamase producing (ESBL+) gram-negative aerobes	[Doripenem ($120–$150) *or* imipenem ($120–$150) *or* meropenem ($210–$240)] ± [amikacin ($5–$10) *or* tobramycin ($15–$20)]	ESBL+ gram-negatives
Septic shock	Unknown site of infection; critically ill patient with central venous catheter in place but not neutropenic or immunocompromised (see Chapter 24)	Vancomycin ($10–$30) + [cefepime ($40–$60) *or* ceftazidime ($30–$60) *or* piperacillin/tazobactam ($80–$100)] + [amikacin ($5–$10) *or* tobramycin ($15–$20)]	Gram-positive cocci MRSA Enterobacteriaceae *Pseudomonas* MDR gram-negative aerobes
	If high local prevalence of ESBL+ gram-negative aerobes	Vancomycin ($10–$30) + [doripenem ($120–$150) *or* imipenem ($120–$150) *or* meropenem ($210–$240)] ± [amikacin ($5–$10) *or* tobramycin ($15–$20)]	See above, but also ESBL+ gram-negatives
	If *Bacteroides fragilis* is possible (i.e., abdominal site)	Preferentially use piperacillin/tazobactam ($80–$100) *or* doripenem ($120–$150) *or* imipenem ($120–$150) *or* meropenem ($210–$240) for gram-negative coverage *or* add metronidazole ($5–$10)	*B. fragilis* Other bowel anaerobes
	If *Candida* spp. is possible (fungal colonization, severe illness, recent and prolonged broad-spectrum antibiotic exposure, previous surgery, dialysis, use of central venous catheters, receipt of total parenteral nutrition, and length of ICU stay)	Add anidulafungin ($225) *or* caspofungin ($425) *or* micafungin ($240)	*C. albicans* Nonalbicans *Candida* spp.
Urinary tract infection (UTI)	Complicated UTI (with bacteremia, anatomic urinary tract abnormality, or urinary calculus)	Ampicillin/sulbactam ($20–$40) *or* levofloxacin ($40–$60)	Enterobacteriaceae *Enterococcus* spp.
	If *P. aeruginosa* or MDR pathogen suspected (see risk factors, above)	Cefepime ($40–$60) *or* ceftazidime ($30–$60) *or* piperacillin/tazobactam ($80–$100)	*P. aeruginosa* MDR gram-negative aerobes
	If high local prevalence of ESBL+ gram-negative aerobes	Doripenem ($120–$150) *or* imipenem ($120–$150) *or* meropenem ($210–$240)	ESBL+ gram-negatives
	If yeast found on urine culture (with clinical evidence of UTI)	Fluconazole ($100–$200)	*Candida albicans*

TABLE 18.5 ■ **Antibiotics and Their Daily Costs* for Common Health Care–Associated Infections in the ICU** (Continued)

Infection	Clinical Situation	Empirical Therapy	Common Organisms
Central venous catheter infections	Not in severe sepsis or septic shock	Vancomycin ($10–$30)	MSSA; coagulase-negative staphylococci or MRSA Enterobacteriaceae *P. aeruginosa*
	In severe sepsis or septic shock	Vancomycin ($10–$30) + [cefepime ($40–$60) *or* ceftazidime ($30–$60) *or* piperacillin/tazobactam ($80–$100)] + [amikacin ($5–$10) *or* tobramycin ($15–$20)]	MSSA; coagulase-negative staphylococci or MRSA Enterobacteriaceae *P. aeruginosa* MDR gram-negative aerobes
	If high local prevalence of ESBL+ gram-negative aerobes	Vancomycin ($10–$30) + [doripenem ($120–$150) *or* imipenem ($120–$150) *or* meropenem ($210–$240)] ± [amikacin ($5–$10) *or* tobramycin ($15–$20)]	See above, but also ESBL+ gram-negatives
	If *Candida* spp. is possible (see risk factors, above)	Add anidulafungin ($225) *or* caspofungin ($425) *or* micafungin ($240)	*C. albicans* Nonalbicans *Candida* spp.
Sinusitis	If *P. aeruginosa* or MDR pathogen not suspected	Ampicillin/sulbactam ($20–$40) *or* [ceftriaxone ($5–$10) + metronidazole ($5–$10)]	Enterobacteriaceae Oral flora MSSA Fungi including *C. albicans*
	If *P. aeruginosa* or MDR organism is suspected (see risk factors, above)	[Cefepime ($40–$60) *or* ceftazidime ($30–$60)] ± metronidazole ($5–$10), *or* piperacillin/tazobactam ($80–$100)]	*P. aeruginosa* MDR gram-negative aerobes
	If high local prevalence of ESBL+ gram-negative aerobes	Doripenem ($120–$150) *or* imipenem ($120–$150) *or* meropenem ($210–$240)	See above, but also ESBL+ gram-negatives
Wound infections	Postoperative GI or GU wound	Ampicillin-sulbactam ($20–$40) *or* cefazolin ($3–$6)	MSSA *Streptococcus* spp. *Enterococcus* spp. Enterobacteriaceae Anaerobes
	If *Pseudomonas* or MDR pathogen suspected (see risk factors, above)	[Cefepime ($40–$60) *or* ceftazidime ($30–$60) or piperacillin/tazobactam ($80–$100)] ± vancomycin ($10–$30)	*P. aeruginosa* MDR gram-negative aerobes

TABLE 18.5 ■ **Antibiotics and Their Daily Costs* for Common Health Care–Associated Infections in the ICU** (Continued)

Infection	Clinical Situation	Empirical Therapy	Common Organisms
	Postoperative sternotomy	Vancomycin ($10–$30)	MSSA Coagulase-negative staphylococci MRSA *Streptococcus* spp. Enterobacteriaceae
Clostridium difficile colitis	Uncomplicated (see Chapters 38 and 60)	Metronidazole ($5–$10)	*C. difficile*
	Severe (if endoscopic evidence of pseudomembranous colitis, *or* ICU treatment, *or* ≥ 2 of the following: age > 60, temperature > 38.3° C, serum albumin < 2.5 mg/dL, or peripheral white blood cell count > 15,000 cells/μL)	Vancomycin (oral) ($60–$120)	*C. difficile*

*Approximate hospital acquisition cost (circa 2008) for the average daily dose (70-kg person with normal renal function).

ESBL+, extended-spectrum beta-lactamase producing; GI, gastrointestinal; GU, genitourinary; IV, intravenous; MDR, multi-drug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-sensitive *S. aureus*.

CENTRAL VENOUS CATHETER–RELATED INFECTIONS

Risk factors for the development of central venous catheter (CVC)–related infections include length of time the catheter is in place, location of central vein used, characteristics of the patient population, and techniques used for insertion, routine dressing, and manipulation. Although a CVC infection is virtually always present when the catheter's exit site shows erythema or purulence, the lack of these signs does not exclude an infection. In fact, most infected CVCs show no gross evidence of infection at their exit site or along their subcutaneous portion. In response to local evidence of a catheter infection, the catheter should be removed and cultured if available in that institution's microbiology laboratory. The traditional method to culture a CVC is to cut off the distal 2 cm of its tip using sterile technique and to send the tip for quantitative or semiquantitative culture (see Chapter 14 for more details). Empirical antimicrobial therapy should then be initiated. Likewise, if an ICU patient is critically ill with severe sepsis or septic shock of uncertain cause, blood cultures should be obtained from two peripheral sites (and through the CVC in certain institutions [see Chapter 14]), all catheters should be removed, their tips cultured, and empirical antimicrobial therapy begun.

URINARY TRACT INFECTIONS

Urinary tract infections occur most frequently in ICU patients who have indwelling urinary catheters (Chapter 14). Urine cultures from these catheters are often difficult to interpret because of improper sample collection technique or frequent catheter colonization, both of which can lead to false-positive culture results. To prevent this, all urine cultures should be sent with an accompanying urinalysis to evaluate for the presence of pyuria (defined as > 10 white blood cells per high-power field). A positive urine culture ($> 10^5$ colony forming units/μL) without associated

pyuria (in the absence of neutropenia) is unlikely to be caused by infection and can be attributed to colonization. Because urine infections in the ICU are usually caused by gram-negative rods and yeasts, a Gram stain of the urine can help direct empirical therapy.

SINUSITIS

The most common risk factor for health care–associated sinusitis is the presence of a nasal tube—for example, a nasogastric, nasotracheal, or nasoenteral tube. The tube not only obstructs the normal mucus drainage from the sinuses directly but also causes mucosal edema, which blocks sinus drainage. Because clinical signs, such as purulent nasal discharge, may be absent, the diagnosis is usually made with imaging studies, such as computed tomography, in patients with persistent fever. Infections can occur with any organism colonizing the oropharynx of ICU patients, including *Pseudomonas aeruginosa,* other gram-negative bacilli, gram-positive organisms, such as *Staphylococcus aureus,* and fungi. Cultures of fluid obtained from the sinus or ostia, but not from the nares, are recommended to direct therapy. Successful treatment of health care–associated sinusitis depends on removal of the obstructing foreign body and an adequate course of appropriate antibiotics.

WOUND INFECTIONS (SURGICAL SITE INFECTIONS)

The risk of postoperative surgical wound infections (also referred to as surgical site infections or SSIs) depends mostly on the American College of Surgeons classification of operative wounds by the level of their bacterial contamination (see Chapter 14, Table 14.E2). Postoperative wound infection rates increase stepwise from the first to the last categories.

Failure to give preoperative antibiotics *appropriately* is an additional risk factor for the development of surgical wound infections. Appropriate antibiotic prophylaxis given *preoperatively* significantly decreases wound infection rates for all operative wound categories. Because adequate tissue levels of antibiotic must be present at the time of the incision in order to prevent infection, antibiotic prophylaxis must be given between 2 hours and 30 minutes *before* the start of surgery. For prolonged procedures, a second dose may be needed. In most cases, continuing antibiotics postoperatively does not decrease infection rates further.

Additional risk factors for postoperative wound infection include increasing age, duration of surgery, duration of hospital stay before surgery (with ICU stays further increasing risk), presence of a malignancy, and emergency procedures. Surgical wound infections can range from an incisional cellulitis to an abscess requiring incision and drainage (see Chapter 14) or necrotizing fasciitis (see Chapter 66).

SEPTIC SHOCK

In critically ill ICU patients with suspected septic shock, the likelihood of infection increases with the severity of the septic response. ICU mortality caused by septic shock from infections ranges from 20% to 80%, depending on the population, the type of infection, and the timeliness and appropriateness of antimicrobial therapy. Because mortality is high even with appropriate antibiotics in ICU patients, the magnitude of the inflammatory response, and not the infection itself, seems to determine the outcome. Thus, continued septic shock does not necessarily imply a failure of antibiotic therapy.

UNEXPLAINED FEVER, LEUKOCYTOSIS, AND SEPSIS

In some cases in the ICU, the cause of fever, leukocytosis, or severe sepsis remains elusive and persistent despite a comprehensive diagnostic evaluation and, in cases of sepsis, empirical

broad-spectrum antibiotic therapy. In such instances, invasive fungal infection with *Candida* species may be considered. Unfortunately, current microbiologic techniques are relatively insensitive and nonspecific for detecting systemic fungal infection. Therefore, risk factors for invasive candidiasis should be considered and, when present, identify patients who may benefit from antifungal therapy. These risk factors include fungal colonization (especially of multiple sites, e.g., urine, skin, sputum or stool), underlying severity of illness, recent and prolonged broad-spectrum antibiotic exposure, previous surgery (especially bowel surgery), dialysis, use of CVCs, receipt of total parenteral nutrition, and length of ICU stay. In these high-risk patients, a trial of either fluconazole or an echinocandin (depending on the underlying hemodynamic and clinical stability of the patient) is warranted.

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CHAPTER 19

Rational Use of Blood Products

Giora Netzer ■ Babak Sarani ■ Vicente H. Gracias ■ John R. Hess

Transfusion of blood products is one of the most common therapies ordered in the intensive care unit (ICU). It is estimated that 4 million patients are transfused a total of 8 million to 12 million units of packed red blood cells (PRBCs) annually in the United States alone. The majority of these transfusions occur in surgical or critically ill patients. Several studies have documented that 20% to 50% of ICU patients receive PRBC transfusions. Patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) get transfused at higher rates, with the frequency of transfusion ranging between 54% and 83%. Furthermore, in addition to anemia, ~40% of critically ill patients have a low platelet count or abnormal coagulation parameters at some point during their ICU stay. Most of these hematologic derangements, however, are asymptomatic.

Numerous studies have shown that outcome is either not changed or often worsened following transfusion. Because of the potential for blood products to immunosuppress and worsen inflammation in critically ill patients, they should be used only when necessary and the potential benefit outweighs the risk. Indeed, the safest transfusion is the one not given. Conversely, because no alternatives exist to the use of blood products, and the various blood components are vital to life itself, they should not be withheld when their use is indicated.

This chapter describes the available evidence on best transfusion practices in the ICU, including a review of the use of recombinant factor VIIa.

Basis for Transfusion of Blood Products: Benefits and Risks

The traditional "10/30" rule—that all patients should be maintained with a minimum hemoglobin of 10 g/dL and a hematocrit of 30%—is obsolete both in theory and in evidence. Outcomes related to transfusion practices are only now being studied in well-designed prospective trials. Although some well-designed trials can be used to formulate guidelines regarding transfusion of PRBC in critically ill patients, there is only a paucity of evidence to help guide which ICU patients benefit from platelet or plasma transfusion. The few data that do exist suggest a similar risk-benefit profile as seen with PRBC transfusion. However, these findings need to be validated by well-designed studies with clinically meaningful outcomes.

RED BLOOD CELL TRANSFUSION

The normal blood volume is 7% to 8% of predicted body weight (PBW). This corresponds to a total blood volume of ~70 mL/kg PBW (≈4.9 L for a 70 kg patient) with a hemoglobin volume of ~30 mL/kg and plasma volume of ~40 mL/kg. This corresponds to a normal hematocrit of 40% to 45% and a normal hemoglobin (Hgb) of 14 to 16 g/dL. Transfusion of red blood cells can help restore both circulating blood volume and oxygen carrying capacity as described by Equations 1 and 2 in Box 9.2, Chapter 9.

Additional online-only material indicated by icon.

BOX 19.1 ■ Physiologic Mechanisms to Increase Oxygen Delivery in Anemia

Mechanisms That Increase Arterial Oxygen Content

Increased production of erythropoietin

Rightward shift of Hgb saturation curve due to increased 2,3-DPG facilitating oxygen "off-loading" at capillary Po_2 (see Appendix A, Figure 1)

Mechanisms That Increase Cardiac Output

Increased heart rate

Increased myocardial contractility

Decreased blood viscosity leading to decreased peripheral vascular resistance (afterload)

Hgb, hemoglobin; 2,3-DPG = 2,3-diphosphoglycerate.

The body has many adaptive responses to increase oxygen delivery in the face of anemia (Box 19.1). Clinicians can increase O_2 delivery by increasing the oxygen saturation or hemoglobin concentration or cardiac output. However, the latter results in increased myocardial oxygen consumption. Although this increases oxygen delivery acutely, a profound or prolonged increase in demand may precipitate ischemia in patients with underlying coronary artery disease.

Historical practice dictated that the ideal target for hemoglobin and hematocrit in hospitalized patients should be 10 g/dL and 30%, respectively. The basis for this target lies in part on rheologic calculations suggesting that this was the level at which there was an optimal balance between oxygen carrying capacity (where high is better) and viscosity (where low is better). Such a balance theoretically would minimize cardiac work while maintaining peripheral oxygen delivery. As recently as the 1990s, this recommendation was supported, in part, by retrospective studies.

GENERAL ICU PATIENTS

Given the need to balance the harmful sequelae of transfusion with the potential benefits of red blood cells in oxygen delivery, Hebert and co-workers reported in 1999 the results of a multicenter, randomized study, the Transfusion Requirements in Critical Care (TRICC) trial, which assessed the clinical impact of a restrictive transfusion strategy versus a traditional transfusion strategy in ICU patients. The restrictive strategy's transfusion threshold was Hgb < 7 g/dL, whereas the liberal's threshold was Hgb < 10 g/dL. When patients in both arms were transfused PRBCs, the volume administered was one unit. Although 30-day mortality (the study's primary outcome) was lower in the restricted transfusion group versus the traditional strategy, it was not significantly different (18.7% versus 23.3%, P = 0.11). However, patients who were transfused by the restrictive strategy had a lower *hospital* mortality compared to those in the traditional transfusion group (22.2% versus 28.1%, P = 0.05). Not only were no adverse outcomes associated with the restrictive strategy, the restrictive strategy utilized fewer PRBCs.

Based on the findings of the TRICC trial, as a general rule, hemodynamically stable and asymptomatic patients in the ICU should not be transfused until their Hgb drops < 7 g/dL, at which point they should be transfused a single unit of PRBCs (Table 19.1). After this one unit is given, the patient's Hgb should be rechecked to determine whether another transfusion is necessary to maintain the hemoglobin level at ≥ 7 g/dL.

Although the TRICC protocol's Hgb threshold of < 7 g/dL for PRBC transfusion has been shown to benefit a population of patients, individuals may manifest varying degrees of tolerance

TABLE 19.1 ■ **Suggested Packed Red Cell Transfusion Thresholds in Patients Who Are Not Actively Bleeding**

Indication	Suggested transfusion threshold
Hemodynamically stable patient	7 g/dL*
Patient with cardiovascular disease	7–8 g/dL*
Septic shock	7–10 g/dL*†‡
Acute coronary syndromes	
Unstable angina, non-STEMI	8–10 g/dL*‡
STEMI	10 g/dL*
Traumatic brain injury	7 g/dL*

*Transfuse only one-unit packed red cells at threshold, then recheck Hgb.
†Pending results for ProCESS study: http://clinicaltrials.gov/ct2/show/NCT00510835, accessed August 2, 2012.
‡See text for details.

to anemia. Should an anemic patient develop anginal pain, electrocardiographic (ECG) changes, or other signs/symptoms of inadequate oxygen delivery, the patient should be transfused, even if his or her Hgb is > 7 g/dL. Conversely, young and otherwise healthy patients may tolerate a Hgb < 7 g/dL. Though the safe and prudent lower limit for this patient population has not yet been defined, both the American Society of Anesthesiologists and the American Red Cross have published guidelines suggesting a lower limit of Hgb 6 g/dL in asymptomatic patients.

STABLE CARDIOVASCULAR DISEASE

In patients undergoing surgery, coronary artery disease appears to reduce the tolerance for anemia, with mortality increasing with greater levels of anemia. For this reason, many espouse a higher transfusion threshold in patients with cardiovascular disease. On the other hand, ~20% of the patients enrolled in the TRICC trial had clinically significant cardiac disease, and no difference in mortality was observed between those transfused with a restrictive versus liberal strategy (20.5% and 22.9%, respectively; P = 0.69). Similarly, a large, randomized clinical trial (n = 2016) evaluating transfusion strategies in high-risk hip fracture patients with cardiovascular disease found no benefit from a liberal (Hgb < 10 g/dL) strategy versus a more restrictive one (Hgb < 8 or symptomatic) in end points of mortality, walking independently, and myocardial infarction.

A 2012 guideline published by the American Association of Blood Banks (AABB) reflected these findings, recommending that asymptomatic patients be transfused at Hgb of 7 to 8 g/dL. Although general recommendations for transfusion triggers can be made (see Table 19.1), an appreciation of a particular patient's physiology and symptoms, as well as an understanding of the inherent risks with transfusion, must be considered.

ACUTE CORONARY SYNDROME

For patients with *acute coronary syndromes* (ACS), there is very little clinical evidence to guide the transfusion threshold, as the TRICC trial excluded these patients and—despite the common presentation of ACS with anemia—a randomized, clinical trial has yet to be conducted. Myocardial oxygen delivery is dependent on coronary artery flow, and one of the physiologic compensations

for anemia is coronary artery vasodilatation. Additionally, increased cardiac output (i.e., increased myocardial work) is another adaptation to anemia. For these reasons, the clinical rationale for transfusion in these patients is that an increase in oxygen carrying capacity should improve myocardial oxygenation in the background of acute coronary events.

Although a single study found that, in older adults, transfusion at a Hgb 10 g/dL was associated with improved survival, two other studies found that in patients with non-ST segment elevation myocardial infarctions (non-STEMI), a Hgb threshold of ~8 g/dL was associated with a trend toward improved outcomes. In all three of these trials, transfusion of patients who were *not* anemic was associated with increased mortality. Although the specific threshold remains to be determined, patients with ACS should be transfused to maintain a higher Hgb than patients with stable coronary artery disease (see Table 19.1). Until a randomized clinical trial provides better guidance, using a transfusion threshold of 8 to 10 g/dL seems reasonable.

EARLY SEPTIC SHOCK

The care of patients with early septic shock was dramatically altered by the paradigm-shifting 2001 publication by Rivers and co-workers. This study found that a multifactorial intervention of hemodynamic goals, including volume resuscitation, vasopressor support, inotropic support, and blood transfusion, dramatically improved survival when administered to patients with severe septic shock within the first 6 hours of presentation. Because blood transfusion was one of several components administered (as a "sepsis bundle"), one cannot ascertain any independent effect that it may have had on outcome. Although many practitioners may transfuse hemodynamically unstable or acidemic patients to a Hgb of 10 mg/dL, the appropriate Hgb level for this patient population has not been determined prospectively. However, Angus and co-workers are conducting a multicenter, randomized controlled clinical trial, the Protocolized Care for Early Septic Shock (ProCESS) study (http://clinicaltrials.gov/ct2/show/NCT00510835, accessed August 2, 2012), which is addressing this important question and whose results should help to provide further guidance.

Beyond the early phase of septic shock, multiple, well-designed studies have failed to show that the transfusion of packed red cells can independently improve oxygen consumption or end-organ oxygen utilization in patients with early sepsis. Additionally, in late septic shock (> 24 hours after presentation), transfusion has not been shown to improve organ perfusion or oxygen consumption by multiple techniques, including gastric tonometry, sublingual microvascular studies, or indirect calorimetry. Because of the immunosuppression associated with transfusion and its strong association with the development of acute lung injury (ALI) and ARDS (with sepsis being the most common etiology of ALI/ARDS), the administration of packed red cells may be harmful. Some clinicians argue, pending the results of the ProCESS study noted previously, that a Hgb threshold of < 10 gm/dL for transfusing the septic patient should not be used (see Table 19.1).

Neurologic Injuries

Of all the debates regarding the optimal strategy for transfusing patients in the ICU, perhaps the most controversial is in those patients with *neurologic injury*. Neurocritical care textbooks have traditionally held to a liberal transfusion strategy (Hgb < 10 g/dL). The TRICC trial did enroll patients with traumatic brain injury (TBI), but this subgroup was too small for meaningful analysis.

In an observational study, anemia was associated with an increased risk of cerebral infarction and death in patients with subarachnoid hemorrhage (SAH). However, transfusing SAH patients does not appear to reduce mortality while, at the same time, increases the risk of acute lung injury. In TBI, transfusion has not been found to reduce in-hospital morbidity or mortality. Three

studies have found that transfusing packed red cells increases cerebral oxygenation ($PbtO_2$) in TBI; however, the significance of these findings is unclear. None of these studies used other volume expanders as a control, and no dose-dependent relationship was seen with the administration of multiple units of transfused blood. Moreover, approximately one quarter of the patients transfused actually had decreases in $PbtO_2$ and, when measured, no effect on neurologic outcomes was observed. These findings can likely be explained by changes in the injured brain's metabolism and circulation (e.g., patients with TBI have low cerebral oxygen extraction and demonstrate a loss of autoregulation). Likewise, vasospasm is one of the prominent pathophysiologic features of SAH. Moreover, brain edema may make oxygen delivery flow dependent rather than diffusion dependent. Thus, the importance and benefit of increasing cerebral oxygen delivery are unclear. For this reason, the American College of Critical Care Medicine Taskforce's Clinical Practice Guidelines concluded that there is no convincing evidence for benefit in a liberal transfusion strategy (Hgb < 10 g/dL) in these patients. Thus, at this time, a restrictive transfusion strategy (Hgb < 7 g/dL) is recommended (see Table 19.1).

Although the majority of evidence suggests that best outcomes are obtained in the nonbleeding patient by minimizing transfusion, the opposite seems true in the setting of active hemorrhage. However, randomized clinical trials to support this conclusion are lacking. The pathophysiology of hemorrhage is more complex than simple hypovolemic shock, as it involves not only prior and ongoing blood loss but also an acquired coagulopathy and the loss of endothelial barrier integrity (Chapter 9). Current best evidence suggests that patients who are bleeding, particularly those with significant blood loss (≥ five units of PRBCs), benefit from more aggressive administration of blood products.

Risks of Transfusion

Transfusion of blood products carries many risks. These include transmission of blood-borne pathogens, transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), and transfusion-related immunomodulation (TRIM).

RED BLOOD CELL TRANSFUSION

Clinically significant transfusion reactions are rare under current guidelines and are most commonly the result of clerical error (Chapter 46). Transfusion-related acute lung injury and TRIM most likely are variants of the same disorder—an exaggerated inflammatory response and altered or deranged immune system resulting from the transfusion of foreign proteins. These syndromes are caused by the spectrum of proinflammatory agents in blood product transfusate, including foreign antigens and antibodies (including anti-HLA and antigranulocyte antibodies), kinins, complement, histamines, and lysophosphatidylcholine. Many of these originate from leukocytes in the transfusate, which can number up to 1 million residual white cells in a unit of packed red cells, even after optimal leukoreduction. Transfusion-related acute lung injury may represent the result of local (pulmonary) inflammation, whereas TRIM may represent systemic immune derangement. Both entities are likely underreported owing to lack of unique diagnostic criteria and adequately designed studies aimed to address their incidence.

TRALI is defined as noncardiogenic pulmonary edema that occurs within 4 hours of transfusion. TRALI has a reported incidence of 1:5000 to 1:10,000 transfusions and is most common following transfusion of plasma. Transfusion-related immunomodulation is best exemplified by reports showing the association between PRBC transfusion and infection and reports documenting a chimeric state where donor leukocytes can be found in the peripheral blood of transfused trauma patients years after the transfusion itself.

One of the first clinical observations of this immunosuppression was made in 1973. In the era before effective immunosuppressive pharmacotherapy, it was noted that multiple transfused renal transplant patients had greater allograft survival than those who were not transfused. The lung may be particularly sensitive to the effects of transfusion, with multiple studies finding an increased incidence of acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) in transfused patients, as well as increased mortality with transfusion in those patients with ALI/ARDS. Co-transfusion of soluble proteins, such as human leukocyte antigen (HLA) or fibrinogen/fibrin degradation products, or co-transfusion of disrupted white blood cell products has been proposed as possible explanations.

PLASMA TRANSFUSION

The plasma portion of donated whole blood contains most of the necessary clotting factors of the coagulation cascade. However, there are minimal concentrations of factors I (fibrinogen), V, VII, and VIII because of degradation and dilution. Fresh frozen plasma (FFP) transfusion is indicated for the correction of coagulopathy from multiple factor deficiencies in the setting of hemorrhage. The causes of these multiple coagulation factor deficiencies include advanced liver disease, warfarin use, and disseminated intravascular coagulation. FFP is typically administered at a dose of 15 mL/kg predicted body weight (PBW), and generally the administration of four units of FFP results in 40% factor replenishment. It is vital to understand this dosing regimen because plasma is frequently underdosed. Most patients require *at least* four units (1 L) of plasma to reverse coagulopathy effectively, assuming that ongoing factor loss, acidosis, and hypothermia are also addressed.

As alluded to earlier, there is wide variability in the manner in which physicians utilize FFP in nonbleeding coagulopathic patients. Many physicians use FFP prophylactically to reverse coagulopathy in nonbleeding patients despite published guidelines recommending against this practice and an unknown risk-benefit ratio. Others cite mild coagulopathy as a reason to use FFP as a volume expander in nonbleeding volume-depleted patients. To date, there are no generally agreed upon guidelines for use of FFP in nonbleeding patients. Suggested indications and dosing are shown in Table 19.2.

Transfusion of plasma has the same risks as transfusion of red blood cells, but the incidence of adverse events is higher for all possible complications. The most frequent adverse event associated with plasma transfusion is TRALI. Some theorize that this reflects variability in plasma protein (and presumably antibody) content in the fluid being transfused. This proposed mechanism is supported by a randomized, blinded, crossover study that found that this risk is higher following transfusion of plasma obtained from multiparous women. One retrospective study found a relative risk of infection of 3 in critically ill surgical patients who received FFP, a finding that is consistent with the risk of infection following PRBC transfusion. Hemolytic transfusion reactions also are possible following transfusion of plasma because plasma contains variable titers of anti-A and anti-B antibody.

CRYOPRECIPITATE TRANSFUSION

Cryoprecipitate is the precipitated fraction obtained by thawing FFP at 4.0° C. This method of isolation means that cryoprecipitate is pooled from the FFP obtained from multiple donors. Cryoprecipitate is rich in factor VIII, von Willebrand factor, factor XIII, and fibronectin. Importantly, it is the only blood component that contains concentrated fibrinogen and thus the main indication for use is in treatment of coagulopathy caused by hypofibrinogenemia. Therefore, it may

TABLE 19.2 ■ **Suggested Fresh Frozen Plasma Transfusion Thresholds in Patients Who Are Not Actively Bleeding**

Indication	Suggested Transfusion Threshold
Nonbleeding patient	No indication at any INR
Thoracentesis, paracentesis	No indication at any INR
Central venous line insertion, lumbar puncture	INR > 1.5
General surgery	INR > 1.5
Neurosurgery	INR > 1.4

be useful in the management of disseminated intravascular coagulation (DIC) with hemorrhage and in reversal of thrombolytic agents (Box 19.2). Dosed adequately, plasma can also be used to replete fibrinogen, but hypofibrinogenemia can be reversed more quickly and with less volume using cryoprecipitate. Cryoprecipitate is typically dosed as a 10-pack transfusion—each 10-pack transfusion raises the serum fibrinogen level by about 60 to 100 mg/dL. Bleeding patients with known von Willebrand deficiency also should receive cryoprecipitate to optimize platelet function, while nonbleeding patients with this disorder can be treated with desmopressin acetate or DDAVP (Chapter 26).

Risks associated with transfusion of cryoprecipitate are the same as those reported for the other blood components. However, the incidence of TRALI and TRIM is probably lower than that associated with transfusion of plasma because the total volume of cryoprecipitate transfused is much less than plasma, minimizing the recipient's exposure to foreign protein antigen. The risk of transmission of blood-borne pathogens, however, may be higher because of the pooled nature of this product. There are no well-designed studies assessing outcomes or adverse events related to transfusion of cryoprecipitate.

PLATELET TRANSFUSION

The need to maintain adequate platelet counts for the prevention of spontaneous bleeding must be weighed against the risks of platelet administration, which includes bacterial contamination, immediate and delayed transfusion reactions, TRALI, and increased risk of developing lung injury. Additionally, the greater the quantity of platelets transfused, the greater the likelihood of alloimmunization, which may result in a patient refractory to future platelet transfusions.

Most randomized clinical trials evaluating platelet transfusion thresholds have been performed in patients with hematologic malignancies (Chapter 24). Although these patients differ from critically ill patients in many respects, rational platelet transfusion strategies can be extrapolated from their data. A transfusion threshold of 10,000/μL has been shown in both observational and interventional studies to be as effective as higher platelet counts in the prevention of spontaneous hemorrhage (Table 19.3). Although some experts recommend maintaining a higher count, such as 20,000/μL, in patients with sepsis or coagulopathy, supportive evidence is limited. Platelet administration prior to invasive procedures is prudent, with a goal count of 40,000/μL, per American Society of Clinical Oncology (ASCO) guidelines. Platelets should not be administered to thrombocytopenic patients with thrombotic thrombocytopenic purpura (TTP) (Chapter 63) or heparin-induced thrombocytopenia (HIT) (Chapter 45) who are not bleeding, because of the high risk of thrombotic and potentially life-threatening complications.

The efficacy of platelet transfusion to reverse the effects of antiplatelet medications is practiced commonly, but remains anecdotal.

BOX 19.2 ■ Indications for Transfusion of Cryoprecipitate

Hemophilia A (factor VIII deficiency)
von Willebrand disease
Fibrinogen deficiency (< 100 mg/dL)
Dysfibrinogenemia
Factor XIII deficiency
Uremic platelet dysfunction
Treatment of bleeding related to thrombolytic therapy

Massive Exsanguination and Transfusion

Patients requiring a massive transfusion are a unique cohort in whom aggressive transfusion is needed for hemodynamic support and reversal of coagulopathy (Table 19.4). A common definition of massive transfusion is transfusion of 10 units of PRBCs within 24 hours. This definition, however, does not direct attention to the ongoing coagulopathy that frequently exists in these patients and further propagates the process underlying the hemorrhage. Published experiences in battlefield transfusions in Iraq, as well as a large observational cohort study of trauma patients in the United States, suggest that an FFP-to-PRBC transfusion ratio of ≥ 1:1.5 improved survival in massively transfused patients, though with an increased incidence of acute lung injury. Because it is difficult to assess the total amount of blood that a patient will require during resuscitation at its start, it seems reasonable to start a ratio of one unit FFP per unit of PRBCs (1:1 ratio) in the briskly bleeding trauma patient. Though this ratio has not been studied in patients with nontraumatic causes of bleeding, the pathophysiology of other forms of hemorrhage share important similarities with bleeding sustained from injury. Additional FFP should be given as necessary to correct an elevated INR to < 1.5. Thus, pending the results of a prospective study to validate these findings, it seems prudent to treat exsanguinating patients with aggressive transfusion of PRBC, plasma, and platelets while also preventing hypothermia, acidosis, and other causes of ongoing coagulopathy. Future studies specifically evaluating optimal ratios of transfusion products and ratio of crystalloid to blood products are needed.

TABLE 19.3 ■ **Suggested Platelet Transfusion Thresholds in Patients Who Are Not Actively Bleeding**

Indication	Suggested Transfusion Threshold
Prevention of spontaneous bleeding	< 10,000/μL
Prevention of spontaneous bleeding in setting of other coagulopathy	< 20,000/μL
Bone marrow biopsy	< 20,000/μL
Paracentesis, thoracentesis, central venous line insertion, lumbar puncture, other invasive bedside procedures	< 40,000/μL
General surgery	< 50,000/μL
Neurosurgery, polytrauma	< 100,000/μL

TABLE 19.4 ■ **Transfusion Guidelines for Patients Who Are Acutely Bleeding**

Clinical Situation	Recommended Response
Rapid acute hemorrhage without immediate control, estimated blood loss > 30%–40%, or presence of symptoms related to severe blood loss (see Box 9.1 in Chapter 9)	Transfuse PRBC. Initiate massive transfusion protocol with 1:1 RBC:FFP*
Estimated blood loss < 25%–30% without uncontrolled hemorrhage	Crystalloid resuscitation, proceed to blood transfusion if hemorrhage is not quickly controlled
Presence of comorbid factors	Consider transfusion with lesser degrees of blood loss

*May require uncrossmatched or type-specific blood.
PRBC, packed red blood cells.

Recombinant Factor VIIa

Recombinant factor VIIa has been approved by the Food and Drug Administration (FDA) for use in hemophiliacs with antibody to factor VIII or IX. However, many case reports and small case series suggest that it also may have a role in arresting or abating hemorrhage from other causes. Recombinant factor VIIa binds to exposed tissue factor in an area of endothelial injury, thereby activating platelets and forming a platelet plug. It then stimulates the coagulation cascade by activating thrombin on the platelet plug. Fibrinolysis is inhibited through factor VIIa–mediated activation of thrombin-activatable fibrinolysis inhibitor.

OFF-LABEL USAGE

Factor VIIa has been shown to decrease or arrest hemorrhage in cases of trauma (after surgical bleeding had been addressed). Two parallel randomized, blinded, placebo-controlled studies found that the drug was associated with a 50% relative reduction in severity of hemorrhage in bluntly injured patients but was not found to have a transfusion-sparing effect in victims of penetrating trauma. However, the doses used in these studies were much higher than the commonly accepted dose of 90 μg/kg PBW, a difference that has substantial cost implications with this expensive drug. The only large, randomized, blinded, placebo-controlled study on the use of factor VIIa in injured patients was stopped early for futility when the control arm was noted to have a substantially lower mortality than anticipated (11% in lieu of 30%). The latter made the study underpowered to detect a mortality difference. However, this study found a decrease in the amount of blood products needed in the treatment arm, with the biggest blood salvaging benefit noted in patients sustaining blunt trauma.

Off-label use of factor VIIa has also been studied in other conditions. Despite initial reports that factor VIIa may decrease the severity of spontaneous intracranial hemorrhage, a large randomized, controlled trial did not find any difference in mortality or neurologic outcome with administration of this drug. In a randomized study, recombinant factor VIIa was shown to decrease the incidence of rebleeding in patients with esophageal varices, but patients required a total dose of 800 μg/kg over 30 hours (i.e., ~900% of the usual dose of 90 μg/kg). This again calls into question the cost-versus-efficacy issue of this agent.

Many case reports and small series suggest that factor VIIa also may be effective in arresting postpartum hemorrhage, but prospective studies are needed to validate these findings.

Lastly, a series of case reports and retrospective reviews suggest that factor VIIa can be used to rapidly reverse the anticoagulant effects of warfarin (which is usually readily reversed by FFP transfusion). However, once again, prospective studies have not been performed to validate these findings or to determine how the reversal impacts on ultimate clinical outcome.

Uncontrolled case series and retrospective reports suggest that factor VIIa is most effective when administered early in exsanguinating patients (i.e., before eight units of PRBCs have been transfused). Further, there are data to suggest that the efficacy of this agent may be markedly diminished in the presence of profound acidosis and coagulopathy (prothrombin time > 17.6 seconds); however, this has not been confirmed in larger studies.

ADVERSE EVENTS ASSOCIATED WITH RECOMBINANT FACTOR VIIA

Recombinant factor VIIa is associated with significant and potentially devastating thromboembolic complications, particularly when used in an off-label fashion. This seems to be especially true in patients > 55 years old, possibly because these patients are likely to have ulcerated plaque (with exposed tissue factor) from atherosclerosis. Reports from the FDA suggest that the incidence of thromboembolic disease is 0.02% when the drug is used in hemophiliacs, but the incidence of

myocardial infarction, stroke, or pulmonary embolism may be as high as 8% when the agent is used off-label in other populations. Moreover, there is an almost equal incidence of arterial and venous thrombi following administration of the drug.

Alternatives to Red Cell Transfusion

Because of clinicians' concerns regarding the potential harm incurred by blood transfusion, as well as the public's concern for its potential (albeit rare) infectious complications, much attention has been directed toward the development and testing of potential alternatives to allogenic erythrocyte administration. The most promising of these was the recombinant preparation of human erythropoietin. Unfortunately, a large, multicenter, placebo-controlled, randomized clinical trial found that erythropoietin alfa administration did not reduce the need for transfusion in critically ill patients. Moreover, its use was associated with an increase in both venous and arterial thrombotic events, a finding seen in previous clinical trials evaluating its use. At this time, erythropoietin use is not recommended for use in the critically ill. Clinicians should not begin this medication de novo in the ICU. Furthermore, given these concerns, for those previously on outpatient erythropoietin for treatment of anemia resulting from malignancy or chronic renal failure, this medication should be held.

Multiple studies have evaluated a variety of synthetic oxygen carriers, including perfluorocarbons and synthetic hemoglobin. However, all of these studies have resulted in increased mortality to those receiving these blood substitutes. The search continues for an alternative to packed red cell transfusion.

Tranexamic Acid

Tranexamic acid (TXA) is a synthetic lysine derivative that inhibits fibrinolysis by binding to and inhibiting plasminogen. A review of 53 studies incorporating 3836 persons undergoing elective operation found that administration of this agent resulted in a 39% decrease in transfusion need. More recently, the CRASH-2 trial, a multinational, randomized, blinded, placebo controlled study that included 270 hospitals and enrolled more than 20,000 injured patients, found that administration of TXA within 8 hours of injury resulted in a statistically significant 1.5% decrease in the risk of death from any cause. Further analysis found that the biggest reduction was hemorrhage-related death. However, subsequent subgroup analysis found that this benefit was confined to patients who received the drug within 3 hours of injury. Persons who received the medication between 3 to 8 hours following injury had a *higher* mortality than the placebo group. The CRASH-3 trial, which uses the same methodology to investigate the role of TXA for moderate to severe traumatic brain injury, is currently ongoing.

SEQUELAE OF LARGE VOLUME TRANSFUSION

Clinicians should anticipate complications of massive transfusion. Because blood is anticoagulated with sodium citrate and citric acid, hypocalcemia can result from the binding of citrate to plasma-ionized calcium. Ionized calcium levels (instead of total calcium levels) should be checked frequently, and hypocalcemia should be treated immediately with either calcium gluconate or calcium chloride, with the latter being the preferred choice. Because citrate is eventually metabolized to bicarbonate, metabolic alkalosis can sometimes result, particularly in patients with renal insufficiency. Additionally, stored erythrocytes release potassium, with the concentration increasing with time and decreased temperature. Profound hyperkalemia can thus result from massive transfusion, particularly when stored blood is administered rapidly.

Blood products are stored by refrigeration or freezing and are often still cold when administered. Because hypothermia can cause or exacerbate coagulopathy, as well as result in cardiac arrhythmias, when large volumes of blood components are transfused, they should always be given through a fluid warmer.

HELPING TO PREVENT TRANSFUSION

As discussed previously, anemia is common in the ICU both because of decreased blood production and well as ongoing blood loss. Although one cannot at this time safely and effectively increase red cell production (with erythropoietin alfa or other agents), one can make some decisions to decrease blood loss. The single most common cause of blood loss in the ICU is through phlebotomy. Each collection tube typically requires 3.5 to 5 mL. Additionally, laboratory specimens collected from a central venous catheter require the prior clearance of infusate, resulting in additional losses of 2 to 10 mL of "waste" blood with each draw. (Consideration should be given to using closed blood conservation systems that are available to allow return of such "waste" blood to the patient.)

Clinicians should always consider the necessity and volume of laboratory specimens that are collected daily and consider their potential impact on patient management and safety. Curtailing or eliminating unnecessary phlebotomy will reduce blood loss and may help to reduce transfusions in critically ill patients.

COSTS OF TRANSFUSION

The physician's foremost responsibility to the patient is to provide appropriate and best care. When best care also results in cost savings, the overall benefit increases, as resources are conserved. Such is the case for best-practice transfusion strategies in the nonhemorrhaging patient (see Table 19.1). Blood products themselves are limited in supply. In addition, these blood products carry a monetary cost to patients, hospitals, and society as a whole. Added to the cost of transfusion are the clinical costs incurred by the many adverse reactions attributable to blood administration.

It is concerning that ICU physicians are not strictly adhering to the restrictive red cell transfusion strategy validated by the TRICC trial. One study concluded that if physicians were to adhere to this strategy in their ICUs, the total savings from reduced packed red cell use and the reduced incidence of red cell transfusion-related complications would be nearly $1 billion U.S. dollars yearly. Physician adherence to evidence-based guidelines for platelet transfusions may increase this cost savings to millions more annually. A judicious approach to transfusion saves lives and money.

An annotated bibliography can be found at www.expertconsult.com.

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This is a large, observational study finding that aggressive FFP transfusion in trauma patients, while increasing the risk of ARDS, decreases mortality.

CHAPTER 20

Renal Replacement Therapy

Sidney Kobrin

Acute kidney injury (AKI) commonly occurs in intensive care unit (ICU) patients. Despite advances in both critical care therapy and renal replacement therapy (RRT), mortality continues to exceed 50% in ICU patients with AKI requiring RRT. When patients develop AKI, the ICU team and consulting nephrologist should collaborate to (1) reverse or prevent progression of AKI (see Chapter 82), (2) initiate renal replacement therapy at an optimal time, (3) choose the RRT modality that best suits the patient's particular circumstances, (4) decide on the dose of solute clearance, and (5) select the ultrafiltration goal. This chapter reviews the thresholds for initiating RRT, the pros and cons of available RRT modalities, the optimal dose of solute clearance, and how to determine the ultrafiltration goal.

When to Start Renal Replacement Therapy

Most authorities would agree that certain signs and symptoms are strong indications for commencing RRT (Box 20.1). The value of early dialysis in asymptomatic patients, however, remains unproved. Some, but not all, uncontrolled and retrospective studies suggest that prophylactic dialysis aimed at maintaining the blood urea nitrogen (BUN) below 80 to 100 mg/dL (28 to 35 mmol/L) reduced mortality and morbidity in patients with AKI. Even two studies using concurrent controls to examine this issue provide contradictory results. The optimal timing for initiation of RRT in asymptomatic patients with AKI will require an adequately powered prospective randomized trial. However, the adequate design of such a trial is limited by the current inability to quickly and prospectively identify patients with early AKI who will have protracted renal injury and eventually require RRT.

Despite the lack of conclusive data, many nephrologists institute early RRT, believing this practice simplifies AKI management, reduces morbidity, and improves patient well-being. Conversely, two arguments can dissuade against the early institution of RRT. First, the hypotension and cytokine release that often accompany RRT may hamper AKI recovery. Second, early RRT may increase costs without providing measurable clinical benefit. Absent convincing studies, the decision to initiate dialysis in asymptomatic patients must be based on clinical judgment alone. For example, no compelling reason exists to commence dialysis in an asymptomatic, normokalemic patient with nonoliguric AKI whose laboratory values reveal a BUN of 100 mg/dL, serum creatinine of 10 mg/dL (800 mmol/L), and slowing in the rate of rise of the BUN and serum creatinine over the preceding several days. Such a patient is likely to recover renal function spontaneously within a few days. However, an unstable patient with oliguric AKI and a recent rapid rate of rise in BUN and serum creatinine is unlikely to recover soon. Described as "hypercatabolic," such patients generate uremic toxins rapidly and frequently accumulate acid and potassium. Intuitively, in this situation RRT should be started before the seemingly inevitable buildup of these dangerous chemicals.

Physicians should exercise caution when using a BUN of 100 mg/dL as a threshold for initiating RRT. BUN can be raised out of proportion to the serum creatinine level, secondary to excessive protein administration, gastrointestinal bleeding, or tetracycline or corticosteroid use. Patients may exhibit a BUN exceeding the 100 mg/dL threshold but lack evidence of uremia

BOX 20.1 ■ Indications for Renal Replacement Therapy in Patients with AKI

Presence of the uremic syndrome
- —Altered mental status (personality changes, confusion, coma)
- —Anorexia, nausea, vomiting
- —Asterixis, myoclonus
- —Pericarditis
- —Seizures

Fluid overload resistant to diuretic therapy
Metabolic acidosis (pH less than 7.1)
- —When additional sodium bicarbonate administration would lead to volume overload

Hyperkalemia refractory to medical therapy
Persistent bleeding secondary to platelet dysfunction
- —When unresponsive to medical therapy (see Chapter 26)

Serum BUN and creatinine*
- —BUN > 100 mg/dL or creatinine > 10 mg/dL

**These are controversial indications in the absence of uremic signs and symptoms or in the absence of their rapid rise in the preceding several days.*

or the need for dialysis. Alternatively, in patients with decreased urea generation caused by poor nutrition or liver disease, manifestations of the uremic syndrome may appear despite a BUN below this threshold.

Available Modalities

A thorough knowledge of the efficacy, advantages, disadvantages, route of access, and cost of each modality is critical when choosing the optimal renal replacement method (Table 20.1). There are three types of RRT therapies: intermittent therapy, continuous therapy, and hybrid therapy. In terms of efficacy, the major considerations are efficiency of solute clearance, volume removal (ultrafiltration), and the impact on patient survival.

INTERMITTENT THERAPIES

Intermittent Hemodialysis

Intermittent hemodialysis (IHD) requires a large-diameter double-lumen central venous catheter for access. IHD uses a semipermeable membrane through which the patient's blood and dialysis solution flow in opposite directions. Solutes are removed largely by diffusion. Advances in dialysis hardware and dialysate solutions allow critically ill patients to tolerate this procedure better than in the past. For example, volumetrically controlled machines permit precise ultrafiltration compared with older machines. Previously, overshooting ultrafiltration goals were common and contributed to the frequent development of hypotension during dialysis. In addition, widespread use of bicarbonate rather than acetate as the dialysate buffer has now reduced the risks of intradialytic hypotension. Despite these advances, hypotension continues to occur frequently during IHD, especially in hemodynamically unstable, critically ill patients receiving large volumes of intravenous fluid between dialyses. Such patients may require in the range of 4 to 6 L of ultrafiltration during a 4-hour dialysis treatment.

The cardiovascular defense mechanisms that normally maintain blood pressure during fluid removal are often impaired, overwhelmed, or both in critically ill patients. Such patients

TABLE 20.1 ■ **Characteristics of Renal Replacement Modalities**

Modality	Abbr.	Solute Clearance (per Day)	Ultrafiltration Capability	Anticoagulation	Cost*
Intermittent Therapies					
Intermittent hemodialysis	IHD	25 L	1+	Systemic is ideal; heparin free or regional is possible	2+
Isolated ultrafiltration	IUF	Negligible	2+	Systemic is ideal; heparin free or regional is possible	1+
Continuous Therapies					
Venovenous Methods					
Venovenous slow continuous ultrafiltration	VV-SCUF	Negligible	3+	Systemic is ideal; regional is very cumbersome	2+
Continuous venovenous hemofiltration	CVVH	15–25 L	3+	Systemic is ideal; regional is cumbersome	4+
Continuous venovenous hemodialysis	CVVHD	24–60 L	3+	Systemic is ideal; regional is cumbersome	4+
Continuous venovenous hemodiafiltration	CVVHD+F	24–70 L	3+	Systemic is ideal; regional is cumbersome	4+
Peritoneal dialysis	PD	12–36 L	2+ – 3+	No systemic anticoagulation is needed	2+
Hybrid Therapies	EDD or SLED	25 L	3	Has been done without anticoagulation	2+

*Cost refers to expenses accrued by the dialysis cost center and does not include extra work by ICU house staff or nursing staff (which would be highest for the continuous venovenous modalities).

frequently exhibit cardiac dysfunction or peripheral vasodilation, for example, secondary to sepsis or liver failure. This hypotension may have many sequelae, including delayed recovery of AKI and ischemia to many organs, including the heart and intestine. Another major disadvantage of IHD is the requirement for a specialized dialysis nurse to devote individual (one-on-one) care to the critically ill patient at the ICU bedside, as opposed to caring for three or four more stable patients in a dialysis unit.

The major advantage of IHD is the most rapid clearance of solutes (including potassium) and correction of metabolic acidosis. Systemic anticoagulation is generally required to prevent clotting of the system during routine dialysis. Heparin-free regimens, however, are available and can be employed to dialyze critically ill patients with active bleeding, after recent surgery, or with suspected or proven heparin-induced thrombocytopenia.

Isolated Ultrafiltration

Isolated ultrafiltration (IUF) resembles IHD and also uses a double-lumen central venous catheter for access. The major difference between IUF and IHD is that dialysate is not pumped through the filter. The pressure settings across the dialyzer are programmed to remove a certain fluid volume. IUF is indicated in fluid-overloaded patients, resistant to diuretics and without significant accumulation of nitrogenous wastes, hyperkalemia, or metabolic acidosis (as solute

removal is negligible). IUF is less likely than conventional IHD to induce intradialytic hypotension. Simultaneous ultrafiltration and solute removal as occurs during standard IHD result in a rapid decrease in intravascular osmolality, which reduces the rate of osmotically induced plasma refilling from the intracellular and interstitial compartments. In contrast, intravascular osmolality remains stable with IUF, the rate of plasma refilling is relatively rapid, and blood pressure is better maintained than during IHD. Another mechanism that contributes to the better hemodynamic stability during IUF, as compared to IHD, is that IUF results in pronounced energy loss from the patient to the extracorporeal circuit. This energy loss results in a lower patient core temperature, which in turn increases peripheral vascular resistance and therefore blood pressure.

Generally, in the presence of peripheral edema and normal blood pressure, patients tend to tolerate ultrafiltration rates of 1 to 2 L/hour. However, the greater the hemodynamic instability, the less likely such rapid ultrafiltration rates will be tolerated.

CONTINUOUS THERAPIES

Continuous renal replacement therapy (CRRT) was historically delivered via an arteriovenous circuit. However, high rates of complications (arterial thrombosis and bleeding) occurred, and the limited blood flow in critically ill hypotensive patients resulted in frequent filter clotting and reduced solute clearance. These problems led to obsolescence of the arteriovenous approach, now virtually entirely replaced by a venovenous approach. Using a single double-lumen central venous catheter for access, the venovenous modalities require a blood pump to provide a constant blood flow independent of the mean arterial blood pressure. Venovenous CRRT machines are similar to IHD machines, with air-leak detectors, pressure monitors, and alarms in the circuit. Variation in the amount of ultrafiltration and use of dialysate allows for four different variations of the procedure (see Table 20.1). The major advantage of continuous as compared to intermittent therapies is that fluid may be removed continuously over 24 hours, creating less stress in hemodynamically compromised patients. There is also less variation in electrolyte and acid base parameters, as serum potassium levels tend to rise and serum bicarbonate tends to decrease during the interdialytic interval of IHD.

Venovenous Slow Continuous Ultrafiltration (VV-SCUF)

The equipment required for VV-SCUF is shown in Figure 20.1. Blood circulates from the "arterial lumen" of a double-lumen catheter placed in a central vein through a filter and returns to the patient through the "venous" lumen of the same double-lumen catheter. No diffusive dialysis takes place because no dialysis solution is used. The limitations are similar to IUF.

The major advantage of VV-SCUF, compared with IUF, is that fluid may be removed continuously over 24 hours, creating less stress in hemodynamically compromised patients. The ultrafiltration rate is accurately controlled by placing a pump on the ultrafiltration line. Ultrafiltration in the range of 4 to 7 L/day is feasible with this therapy. Trained dialysis nurses are not required to be at the bedside; ICU nurses generally perform much of the procedure. The nephrologist and ICU team should meet daily and decide on the ultrafiltration goal. This is usually equal to the anticipated daily fluid administration that day minus any fluid losses (from urine, stool, fistulas, ostomies, drains, etc.) plus any net ultrafiltration deemed necessary. Replacement fluid is not required, but all intravenous fluids should contain a physiologic electrolyte composition.

Continuous Venovenous Hemodialysis (CVVHD)

The circulatory access and equipment required for CVVHD are similar to VV-SCUF, with the major addition of dialysate infused in a direction countercurrent to the blood flow (see Figure 20.1). Small solutes—for example, BUN—diffuse from the blood into the dialysate and reach concentrations in the dialysate similar to those in blood. Equilibration between blood and

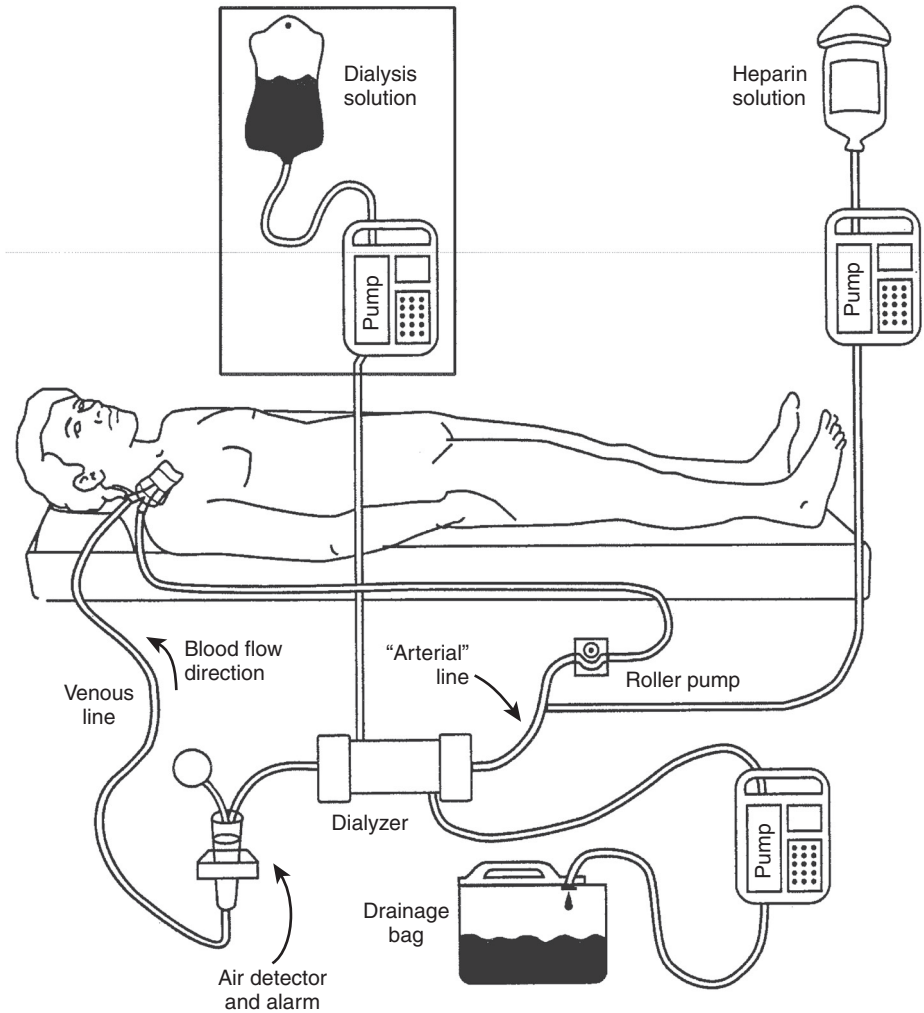


Figure 20.1 The equipment and circuit required for venovenous slow continuous ultrafiltration (VV-SCUF). The additional equipment required to perform continuous venovenous hemodialysis (CVVHD) is shown in the boxed area. The "arterial" line also normally has a pressure transducer in-line (omitted from figure) between the roller pump and the dialyzer to monitor perfusion pressure. *(Modified from Daugirdas JT, Ing TS: Handbook of Dialysis. Boston: Little, Brown, 1988.)*

dialysate persists with dialysate flows up to 30 mL/min (1800 mL/hour). Although equilibration may be less than 100% above this dialysate flow rate, very efficient clearance occurs even with flow rates of up to 65 mL/min (4 liters per hour). Of note, these dialysate flow rates are still much slower than conventional IHD where flow rates of 600 to 800 mL/min are typical. A pump placed on the dialysate outflow line allows accurate control of ultrafiltration, similar to that described for VV-SCUF. Replacement fluid is generally not required because the composition of dialysate electrolytes and minerals is similar to that of normal plasma, creating only a negligible net loss of these substances. However, depending on the dialysate used, the duration of therapy and nutritional support prescribed, hypokalemia, hypocalcemia, and, in particular, hypophosphatemia may each

develop. Therefore, these parameters must be monitored regularly and intravenous replacement infusions given if they fall below physiologic levels.

The slow and continuous ultrafiltration of CVVHD is less likely to cause hypotension than IHD. The daily solute removal with CVVHD is comparable to the usual 4-hour IHD treatment (see Table 20.1).

Continuous Venovenous Hemofiltration (CVVH)

Continuous venovenous hemofiltration (CVVH) resembles VV-SCUF (see Figure 20.1). The goal of this therapy is to achieve the desired volume of net ultrafiltration similar to that described for VV-SCUF while simultaneously clearing solutes. Solute clearance is purely convective, with no dialysate solution administered. The ultrafiltrate resembles that of plasma water so that if 25 L of ultrafiltrate are generated per day, approximately 25 L of blood are cleared of uremic solutes. Replacement fluid of composition similar to plasma water must be administered to prevent volume depletion and replace essential solutes. The net desired ultrafiltration volume for the day is decided in advance, and the volume of replacement fluid is calculated to achieve this goal (Table 20.2).

The major disadvantage of this system is that the hematocrit increases within the filter with high filtration rates, which may predispose to filter clotting. This effect can be reduced by increasing the blood flow rate and by administering the replacement fluid "prefilter" to dilute the blood and attenuate any hematocrit rise. Some investigators claim that administering the replacement fluid prefilter allows time for urea diffusion from red cells into the fluid, thereby increasing urea clearance. However, others believe the administration of fluid prefilter does not increase solute clearance and effectively wastes about 15% of administered fluid. The only potential advantage of CVVH over CVVHD is theoretic, as convective clearance may enhance "middle molecule" (in the midrange of molecular sizes, from about 5000 to 30,000 kDa) clearance, including many known proinflammatory mediators of sepsis (and the systemic inflammatory response syndrome, or SIRS). However, at present there is no evidence that clearance of these mediators improves either the clinical course or survival in sepsis. Similar clearance of small solutes and net ultrafiltration can be achieved with CVVHD. Because there is less rise in the hematocrit along the filter with CVVHD (given the lower filtration volume required with this modality), filter life span may be prolonged and consequently CVVHD is generally the modality of choice when CRRT is required for solute clearance.

Continuous Venovenous Hemodiafiltration

Continuous venovenous hemodiafiltration (CVVHD+F) is simultaneous CVVHD and CVVH. Dialysate is pumped countercurrent to blood as with CVVHD, and ultrafiltration is allowed to

TABLE 20.2 ■ **Sample Dialysis Orders for Continuous Veno-Venous Hemofiltration, Continuous Veno-Venous Hemodialysis, and Continuous Veno-Venous Hemodiafiltration to Achieve 4 L of Net Ultrafiltration and 25 L of BUN Clearance/24 h in a Hypothetical Patient Receiving 4 L of Maintenance IV Fluid/Day**

Order	Continuous Veno-Venous Hemofiltration	Continuous Veno-Venous Hemodialysis	Continuous Veno-Venous Hemodiafiltration
Total ultrafiltration rate	25 L/24 h	8 L/24 h	15 L/24 h
Dialysate flow rate	None (not applicable)	17 L/24 h	10 L/24 h
Replacement fluid flow rate	17 L/24 h	None	7 L/24 h

BUN, blood urea nitrogen.

reach rates of 12 to 24 L/day as with CVVH. Solute clearance is therefore by both diffusion and convection, and it is very efficient, easily approaching 48 L/day. In contrast to CVVHD, CVVHD+F requires replacement fluid and keeping track of fluid balance is more complex. Although CVVHD+F achieves a modest increase in solute clearance, it is rarely necessary and many clinicians believe it is usually not worth the extra effort, expense, and increased potential for human error. Orders for achieving certain levels of solute removal and ultrafiltration in CVVH, CVVHD, and CVVHD+F are illustrated in Table 20.2.

HYBRID THERAPIES

Various techniques have evolved that are hybrids of IHD and CRRT. Two major factors contributed to the introduction of this therapy: the specialized equipment and the 24-hour staffing requirements for CRRT.

Centers unable to acquire the specialized CRRT equipment have modified conventional IHD regimens to provide 8 to 12 hours of treatment per day. When conventional IHD machines are used for this purpose, the dialysate flow is reduced to 100 mL/min (from 600 to 800 mL/min used with conventional IHD). This approach can be applied for 8 to12 hours per day (or nocturnally) because the solute clearance is high and the daily ultrafiltration needs can frequently be realized in this 8- to 12-hour period. Two terms have been used for this hybrid dialytic intervention: extended daily dialysis (EDD) and sustained or slow low efficiency dialysis (SLED).

In many centers, CRRT or EDD requires a change in ICU nursing staffing from a ratio of one nurse to two ICU patients to a one-to-one ratio. When hospitals cannot provide the increased number of nurses to cover CRRT for 24 hours per day, EDD/SLED can be utilized or the CRRT equipment can be used over a 12-hour shift. When using CRRT for 12 hours per day, dialysate or convective clearance flow rates are prescribed at twice the rate of 24-hour therapy, thereby providing similar solute clearance over a 24-hour period. The ultrafiltration goal for the day is condensed into 12 hours. This duration of therapy theoretically offers better hemodynamic stability than conventional 4-hour IHD (especially when IHD is done every other day), and several studies have shown similar hemodynamic stability and pressor requirements as compared to 24 hours of CRRT.

Peritoneal Dialysis

Peritoneal dialysis (PD) involves the insertion of a PD catheter, either percutaneously (with or without peritoneoscopy) or surgically (using a limited "open" technique). Dialysate is then infused, allowed to dwell, and drained. Adjusting the dwell time length and the dialysate glucose concentration results in ultrafiltration rates similar to those of the "blood-based" dialytic procedures (see Table 20.1). Depending on the dialysate volume and dwell time, solute clearance may vary between 12 and 24 liters per day, which may be adequate for relatively stable patients but insufficient for the requirements of critically ill catabolic patients. The major advantages include no vascular access requirement, no need for systemic anticoagulants, and fluid removal can be distributed over 24 hours. The latter should produce greater hemodynamic stability compared with IHD. Unfortunately, PD may not be feasible in patients with recent abdominal surgery because dialysate leakage will result, or in patients with severe pulmonary dysfunction because the dwelling peritoneal fluid can interfere with descent of the diaphragm and lung expansion.

Factors Influencing Selection of a Specific Modality

PATIENT SURVIVAL AND RECOVERY OF KIDNEY FUNCTION

As described earlier, a large number of modalities are available for RRT. When choosing between the available modalities, two main outcomes should influence the modality choice,

namely patient survival and recovery of renal function. Unfortunately, there is a paucity of evidence to guide clinicians.

With regard to patient survival, when choosing a modality it is reasonable to examine the available literature to compare IHD versus CRRT, hybrid therapy versus IHD or CRRT, PD versus IHD or CRRT, and CVVH versus CVVHD.

IHD versus CRRT

Advocates for CRRT claim several advantages compared with IHD: enhanced hemodynamic stability; increased net salt and water removal; enhanced clearance of inflammatory mediators, which may provide benefit in septic patients, particularly using convective modes of continuous therapy; in patients with brain injury or fulminant hepatic failure, continuous therapy may be associated with better preservation of cerebral perfusion.

However, despite these theoretic advantages of CRRT, the available literature does not support a survival advantage over IHD. The majority of studies comparing CRRT and IHD have been observational or retrospective case series, with no survival benefit associated with CRRT after adjustment for severity of illness. Of greater importance, four prospective randomized studies that compared outcomes of AKI supported using either IHD or CRRT found no differences in survival (see Mehta et al and Vinsonneau et al in the bibliography). Five meta-analyses also compared outcomes with CRRT and IHD and were unable to demonstrate a survival benefit attributable to either modality.

With regard to the other important outcome, recovery of renal function, results also appear similar with CRRT and IHD. Although some studies report better recovery with CRRT, these reports only evaluated renal recovery in patients who survived, thereby failing to account for mortality differences between groups. When the analysis combined mortality and nonrecovery of renal function, both groups show similar recovery of function.

Hybrid Therapy versus IHD or CRRT

Although "hybrid therapies" have been shown to have similar hemodynamic effects and provide similar metabolic control as CRRT, there are no data comparing outcomes to either IHD or CRRT.

PD versus IHD or CRRT

There have been no studies comparing peritoneal dialysis and IHD. A single prospective study compared seventy Vietnamese patients with AKI assigned to either PD or CVVH. A markedly increased risk of death was observed among the group administered PD (47% versus 15%). Possible reasons for the poorer survival in the PD group include lower overall creatinine clearance and the use of acetate (lactate is typically used in the United States) as the PD dialysate buffer. Extrapolation from this study is limited as the study population and dialysis technique were very different from that encountered in most developed countries.

CVVH versus CVVHD

Theoretically, convective therapy delivered by CVVH may enhance clearance of proinflammatory mediators when compared to diffusive clearance provided by CVVHD. However, convective clearance may also remove beneficial anti-inflammatory mediators. In addition, the maximal achieved extracorporeal clearance of these mediators is low relative to the rates of generation and endogenous clearance. To date, no randomized studies show superior survival with CVVH therapy as compared to CVVHD.

Other Factors That May Influence Modality Choice

In addition to patient survival and recovery of renal function, other factors that may influence the modality choice include acid-base and electrolyte abnormalities, anticoagulation, and nurse and physician expertise.

ACID-BASE AND ELECTROLYTE ABNORMALITIES

Severe hyperkalemia unresponsive to medical therapy requires rapid correction. IHD is the procedure of choice in this situation because high potassium clearance rates on the order of 200 mL/min are possible. In contrast, CRRT is much less efficient, with maximal clearance rates of only 40 to 60 mL/min. In some circumstances, one may use a single IHD treatment to achieve normokalemia and then switch to a continuous modality to maintain normokalemia and to meet additional dialysis and ultrafiltration needs.

CRRT and PD may be ideal for management of metabolic acidosis in shock states and other patients with sustained lactic acid production. Acidosis increases between IHD sessions, whereas the continuous modalities provide a steady, uninterrupted correction of acidosis. The continuous modalities may also facilitate the administration of large volumes of intravenous bicarbonate because ongoing ultrafiltration can remove the extra volume administered and thereby prevent the development of progressive volume overload.

ANTICOAGULATION

In some patients undergoing CRRT, frequent filter clotting may necessitate systemic anticoagulation, and heparin is the anticoagulant of choice. However, with some commercially available equipment, an average anticoagulation-free filter life span exceeding 30 hours can be achieved. The requirement for systemic anticoagulation is a potential disadvantage because many critically ill patients may have strong contraindications for heparin exposure or anticoagulation. In such patients, regional anticoagulation using protamine or citrate may obviate the need for systemic anticoagulation, although these techniques are relatively cumbersome. They also add another level of complexity to the procedure, further increasing the risk of human error, particularly when the technique is used infrequently. In contrast, PD and IHD can both be performed without the need for systemic heparinization.

NURSING AND PHYSICIAN EXPERTISE

The choice of modality also depends on the experience of the ICU medical and nursing team. Complicated procedures, such as CRRT, should not be undertaken unless a core of dedicated and interested physicians and nurses undergo extensive training in the procedure and set up protocol manuals, support mechanisms, and quality improvement programs. Some suggest that an institution should perform a minimum of 12 procedures annually in order to maintain proficiency in a technique. Certainly, the number of procedures should be estimated before starting such a program. If achieving the minimal number is unlikely, patients needing complicated forms of RRT should continue to be transferred to a center (or an ICU) with an established program.

SUMMARY AND RECOMMENDATIONS REGARDING CHOICE OF MODALITY

Data do not support the superiority of any one particular mode of RRT in patients with AKI. Therefore, selection of a modality should be based on local expertise and the availability of staff and equipment. However, CRRT may be theoretically advantageous in certain clinical scenarios, such as better preservation of cerebral perfusion in patients with fulminant hepatic failure or acute brain injury. In clinical practice, despite the absence of evidence supporting superior patient survival, many nephrologists and intensivists continue to appreciate greater hemodynamic stability with CRRT compared to IHD. Our institution follows the strategy used by the Department of Veterans Affairs/National Institutes of Health's (VA/NIH) Acute Renal Failure Trial Network (ATN) study investigators, where IHD or CRRT was allocated depending on the cardiovascular Sequential Organ Failure Assessment (SOFA) score (Table 20.3).

TABLE 20.3 ■ **Sequential Organ Failure Assessment (SOFA) Score**

Level	Hemodynamic Assessment	Initial RRT
Level 0	Mean arterial pressure (MAP) > 70 mm Hg, no administration of vasopressors	IHD
Level 1	MAP < 70 mm Hg, no administration of vasopressors	IHD
Level 2	Dopamine ≤ 5 μg/kg/min OR any dose of dobutamine	IHD
Level 3	Dopamine > 5 μg/kg/min OR epinephrine ≤ 0.1 μ/kg/min OR norepinephrine ≤ 0.1 μg/kg/min	CRRT or daily SLED
Level 4	Dopamine > 15 μg/kg/min OR epinephrine > 0.1 μg/kg/min OR norepinephrine > 0.1 μg/kg/min	CRRT or daily SLED

The SOFA score is calculated daily, and the original modality continued if the SOFA score remains unchanged.
In patients initially on IHD, therapy is switched to CRRT or daily SLED if the SOFA score increases to 3 to 4.
In patients initially on daily SLED or CRRT, therapy is switched to IHD if the SOFA score decreases to 0 to 1.

Optimal Dosing of Solute Clearance during RRT

The optimal solute clearance prescription had been controversial since the inception of RRT. Two large randomized prospective trials, the ATN Study and the Randomized Evaluation of Normal versus Augmented Level of RRT (RENAL) Study, provide information regarding solute clearance targets for IHD and CRRT.

IHD

The largest prospective randomized study to date examining the impact of IHD dosing on patient survival is the ATN Study. Kt/V is an index of solute removal, where K is the clearance of the dialyzer, t is the duration of therapy during each dialysis session, and V is the volume of distribution of urea for the patient. The ATN study compared IHD delivered six times per week with a target Kt/V of 1.2 to 1.4 per treatment, to IHD delivered three times per week with the same target Kt/V per treatment. There was no statistically significant difference in survival between the two regimens. Therefore, a thrice-weekly regimen with a target Kt/V of 1.2 to 1.4 per treatment is currently recommended. More frequent therapy may be required in selected patients, such as those who have refractory hyperkalemia (see Chapter 39). Additional IUF therapy may be required between conventional dialysis treatments in patients who remain volume overloaded or become hypotensive with three times per week IHD.

CRRT

Conflicting survival results have been reported in several randomized controlled trials comparing low- versus high-dose clearance. The two largest studies to examine this issue both failed to demonstrate a statistically significant difference in survival between lower and higher doses of clearance during CRRT. The ATN study compared outcomes between 20 mL/kg per hour and 35 mL/kg per hour; and the RENAL study randomly assigned patients with AKI to CVVHD+F at an effluent flow of either 25 or 40 mL/kg per hour. Based on these two studies, it is recommended that CRRT be provided with an effluent flow rate of 20 to 25 mL/kg per hour.

An annotated bibliography can be found at www.expertconsult.com.

Bibliography

Bellomo R, Cass A, Cole L, et al: Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 361:1627-1638, 2009.

This study compared 90-day mortality among critically ill patients with AKI who were randomly assigned to CRRT with an effluent flow of either 40 mL/kg/h (high intensity) or 25 mL/kg/h (lower intensity). Higher-intensity CRRT did not reduce mortality at 90 days.

Berbece AN, Richardson RM: Sustained low-efficiency dialysis in the ICU: cost, anticoagulation, and solute removal. Kidney Int 70:963-968, 2006.

This observational, prospective pilot study compared SLED (23 patients, 165 treatments) with CRRT (11 patients, 209 days), focusing on cost, anticoagulation, and small solute removal. Equivalent renal clearance was 29+6 mL/min for SLED, similar to that for CRRT. SLED was routinely performed without anticoagulation and provided solute removal equivalent to CRRT at significantly lower cost.

Davenport A: Continuous renal replacement therapies in patients with liver disease. Semin Dial 22:169-172, 2009.

Hypotension during RRT compromises cerebral perfusion, which can exacerbate cerebral edema in cases of fulminant hepatic failure and those with encephalopathy resulting from chronic liver failure. CRRT causes less cardiovascular and cerebrovascular instability compared to other modalities, and as such is the treatment of choice for this group of critically ill patients.

Kielstein JT, Kretschmer U, Ernst T, et al: Efficacy and cardiovascular tolerability of extended dialysis in critically ill patients: a randomized controlled study. Am J Kidney Dis 43:342-349, 2004.

This study demonstrated that hybrid dialysis combines excellent detoxification with cardiovascular tolerability, even in severely ill patients in the ICU.

Mehta RL, McDonald B, Gabbai FB, et al: A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. Kidney Int 60:1154-1163, 2001.

A multicenter, randomized, controlled trial was conducted comparing two dialysis modalities (IHD versus continuous hemodiafiltration) for the treatment of AKI in the ICU. There was no evidence of a survival benefit of continuous hemodiafiltration compared with IHD.

Palevsky PM, Zhang JH, O'Connor TZ, et al: The VA/NIH Acute Renal Failure Trial Network: intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 359:7-20, 2008.

This trial compared less intensive therapy (IHD and SLED that were given three times per week while less intensive CRRT was given with a flow rate of 20 mL/kg/h) with more intensive therapy (CRRT flow rate of 35 mL/kg/hr). The death rate at day 60 was similar for both groups (53.6% with intensive therapy and 51.5% with less intensive therapy). Likewise, the RRT duration and the rate of recovery of kidney function or nonrenal organ failure were similar for both treatment arms.

Tolwani A: Continuous renal-replacement therapy for acute kidney injury. N Engl J Med 367:2505-2514, 2012.

This is a concise review of CRRT in the context of managing a case of AKI.

Vinsonneau C, Camus C, Combes A, et al: Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. Lancet 368:379-385, 2006.

This study compared IHD to CVVHD+F on survival rates in critically ill patients with AKI as part of multiple-organ dysfunction syndrome. The survival rate at 60 days did not differ between the groups (32% for IHD versus 33% for CRRT).

CHAPTER 21

Rehabilitation Interventions and Recovery from Critical Illness

Daniel Malone ■ Miriam Segal

Although the profound adverse effects of immobility and deconditioning are well documented, confinement to a bed in the intensive care unit (ICU) is common. Often the needs to maintain functional status and physical activity levels are overshadowed by activities geared toward treating critical illness or injury and achieving medical stability. In the ICU, rehabilitation interventions are focused on mitigating the effects of immobility and ICU-acquired weakness (e.g., critical illness polyneuropathy and myopathy [see Chapter 48]) as quickly as possible to diminish untoward, lasting effects. Recovery from critical illness is a process of progressive rehabilitation involving a multidisciplinary team and a variety of treatment modalities and interventions. Rehabilitation interventions complement the highly technologic, lifesaving ICU therapies and are essential for the patient's full functional recovery.

Starting Rehabilitation in the Intensive Care Unit

Rehabilitation emphasizes an interdisciplinary approach (Table 21.1). Its primary goal is the maintenance and restoration of patients' functional independence. There is increasing evidence supporting the importance of early and comprehensive rehabilitation as an integrated aspect of the acute recovery period rather than as the final stage of the recovery process. This approach comprises several elements: (1) an initial and ongoing functional assessment, (2) ongoing interventions to prevent and to address functional loss, and (3) formulation of a longer-term treatment plan to ensure continuation of functional recovery. Optimally, rehabilitation begins as soon as life-threatening instability has passed, although preventive measures can be instituted upon admission to the ICU to prevent the deconditioning syndrome as well as other consequences of immobility.

During critical illness, the initial functional assessment is usually performed by physical and occupational therapists as well as speech language pathologists. As these therapists examine the patient and apply their interventions, functional status is continuously reassessed and documented (Table 21.2). This process often yields another dimension of clinical data, as the early trajectory of patients' functional recovery can be observed and used to predict the extent and pace of further recovery. As patients initially attempt to mobilize, signs of neurologic or neuromuscular dysfunction, such as changes in muscle strength, muscle tone, and coordination of movement patterns, may first become apparent. These alterations can be tracked serially at the bedside using standard assessment tools such as the Medical Research Council (MRC) Scoring System (Table 21.3). Consultant physiatrists (physicians specializing in rehabilitation medicine) then integrate information resulting from the rehabilitation team's assessments with the other clinical data to guide the team's interventions, suggest possible pharmacologic or nursing interventions, apply diagnostic testing, and aid in the determination of a rehabilitation plan upon discharge from the ICU.

Additional online-only material indicated by icon.

TABLE 21.1 ■ **Members of the Multidisciplinary Rehabilitation Team**

Team Member	Description of Roles and Areas of Expertise
Physiatrist (rehabilitation physician)	Medical specialist in disability who provides consultations regarding prognosis and rehabilitation needs, orchestrates rehabilitation services, develops and is responsible for implementation of the multidisciplinary care plan, and prescribes durable medical equipment
Physical therapist (PT)	Health care professional who develops treatment plans to optimize movement, balance, and strength to restore physical function and prevent disability
Occupational therapist (OT)	Health care professional who focuses on activities of daily living, movement impairments of the upper extremity, and cognitive remediation
Speech and language pathologist (SLP)	Health care professional who performs clinical swallowing evaluation, promotes enhanced communication in patients with artificial airways, and provides cognitive remediation to achieve meaningful communication (see Chapter 22)
Case manager or social worker	Identifies posthospital medical, surgical, rehabilitation, and social services based on expected recovery, treatment priorities, health insurance, and personal finances; identifies members of patient's social network to provide support, personal care, and transportation

TABLE 21.2 ■ **Examples of Activities of Daily Living (ADLs) and Functional Skills Addressed by the Rehabilitation Team**

Self-Care	Mobility	Communication and Cognition
Eating	Bed mobility (e.g., rolling, repositioning, supine to sitting)	Hearing
Drinking	Balance in sitting/standing	Vision
Bathing, grooming, dressing, prosthetic management	Out-of-bed activities and transfers (e.g., bed to chair/wheelchair, use of commode or toilet)	Speech/language (e.g., speaking valves, writing, talking, comprehension)
Bowel and bladder control	Ambulation with or without assistive devices	Attention, memory, problem solving, reasoning, safety awareness
Toileting	Wheelchair management	Orientation

Oftentimes, ICU physicians, along with the help of other specialists, must formulate specific precautions and parameters and communicate them to therapists. Examples of this include limiting range of motion or weight bearing after orthopedic procedures and giving clearance for spinal motion and out-of-bed activities after spinal injuries. It is important that this type of communication occur in an efficient manner in order to advance the rehabilitation process.

Specific Rehabilitation Problems and Their Interventions in the Intensive Care Unit

DECONDITIONING

Deconditioning is a syndrome of potentially reversible anatomic and physiologic changes resulting from physical inactivity or placement within a less demanding physical environment.

TABLE 21.3 ■ **Medical Research Council (MRC) Scoring System for Muscle Strength**

Score	Description	Movements Assessed	
		Upper Extremity	**Lower Extremity**
0	No visible contraction		
1	Visible muscle contraction, but no limb movement		
2	Active movement, but not against gravity	Shoulder abduction	Hip flexion
3	Active movement against gravity	Elbow flexion	Knee extension
4	Active movement against gravity and resistance	Wrist extension	Ankle dorsiflexion
5	Active movement against full resistance		

Maximum score: 60 (four limbs; 3 movements per extremity with maximum score of 15 points per limb)
Minimum score: 0 (quadriplegia)
Adapted from Schweickert WD, Hall J: ICU-acquired weakness. Chest 131:1541-1549, 2007.

Hospitalization, regardless of admitting diagnosis, is a major risk for older persons and is often followed by an irreversible decline in functional status and a change in quality of life. Physiologically, changes caused by inactivity are diverse and involve multiple body systems including the musculoskeletal, cardiovascular, and pulmonary systems, as well as body and blood composition, and central nervous, endocrine, and integumentary systems (see Tables 21.E1 and 21.E2). The most apparent effects of prolonged immobilization are declines in the functional reserve of the musculoskeletal and cardiovascular systems as evidenced by muscular atrophy and loss of cardiovascular endurance. The magnitudes of these reductions are dependent on the duration of bed rest confinement, and prior musculoskeletal and cardiorespiratory fitness. Muscle and bone tissue adapt to the decreased loading of bed rest within a matter of days. Although atrophy accounts for most of the decrease in strength, also compromised is the ability to activate muscle via neuromuscular transmission and electrical contraction coupling. Central to the changes in the musculoskeletal system are the lack of usual weight-bearing forces and the decrease in number or magnitude of muscle contractions, or both, especially in the postural musculature. Because the complications attributed to immobility can prolong the ICU or hospital stay, early, graduated, and aggressive remobilization of the patient within the limits of medical and surgical precautions should be the current standard of practice. These organ-specific complications of inactivity require specific preventive and restorative treatments (see Tables 21.E1 and 21.E2).

Although not a new concept, several studies have determined that early mobilization and progressive activity are safe for critically ill patients in the ICU, even those on ventilators, resulting in enhanced out-of-bed (OOB) frequency, increased upright weight bearing, and improved functional mobility, and they may potentially expedite weaning from mechanical ventilation and influence both ICU and hospital length of stay (LOS).

Based on cardiac, respiratory, and neurologic factors, the criteria in Table 21.4 can guide ICU practitioners in knowing when patients can initiate rehabilitation activities in general as well as when an individual rehabilitation session should stop.

COGNITIVE DEFICITS

Critically ill patients often exhibit cognitive deficits that are clinically significant and also impact functional status. Although some patients may be overtly disoriented, others may have significant cognitive dysfunction that becomes apparent only when the matter is probed more specifically. Mental status screening tools, such as the Mini–Mental Status Examination (MMSE) (see Figure 21.E1), can be helpful to assess cognition. Several other disease-specific tools—for example, the

TABLE 21.E1 ■ **The Deconditioning Syndrome: Musculoskeletal and Integument Changes**

Primary Effects on Organ System	Related Complications	Prevention and Treatment Interventions
	Musculoskeletal	
Muscle weakness and atrophy	Decreased strength, coordination, and balance. Increased fall risk	Strengthening exercises; progressive mobilization (sitting/out of bed [OOB], standing, ambulation); electrical stimulation
Joint contractures	Impedes self-care and mobilization	Range-of-motion exercises with terminal stretch, proper positioning of limbs, sometimes with static splinting
Osteoporosis	Pathologic fractures	Weight-bearing and strengthening exercises; progressive mobilization
	Integument	
Subcutaneous tissue ischemia	Pressure ulcers (see also Chapter 42)	Optimize nutrition
Skin atrophy		Frequent repositioning, specialized beds, mattresses, and seat cushions that distribute pressure away from bony prominences
		Avoid shear stress when moving patient

TABLE 21.E2 ■ **The Deconditioning Syndrome: Cardiovascular, Pulmonary, and Metabolic Changes**

Primary Effects on Organ System	Related Complications	Prevention and Treatment Interventions
Cardiovascular		
Hypovolemia/diminished baroreceptor sensitivity/decreased vascular smooth muscle tone	Postural hypotension	Graduated sitting and standing protocols; fluid management
Reduced stroke volume/tachycardia at rest and during submaximal exercise/ reduced maximal cardiac output	Decreased oxygen consumption ($\dot{V}O_2$)/poor cardiovascular endurance	Progressive mobilization and strengthening exercises
Hypercoagulable blood	Deep venous thrombosis (DVT)	DVT prophylaxis including mobilization
	Pulmonary embolism	
Pulmonary		
Reduced pulmonary compliance/ decreased ventilation/regional changes in ventilation/perfusion	Atelectasis/poor cough effort/retained secretions/ potential impaired gas exchange	Airway clearance techniques (e.g., chest wall percussion/vibration)/ deep breathing exercises/ progressive mobilization/ inspiratory muscle training
Respiratory muscle weakness	Prolonged mechanical ventilation	
Endocrine and Metabolic		
Insulin receptor resistance	Glucose intolerance	Serum glucose monitoring
Increase in serum parathyroid hormone	Osteoporosis	Monitor serum calcium
Increased daily nitrogen loss and associated hypoproteinemia	Proteinuria	Optimize fluid and nutritional intake
Negative calcium balance with normal serum levels	Hypercalciuria	Mobilization
Decrease in total body phosphorus, sulfur, sodium, and potassium primarily the result of muscle atrophy	Loss of lean body mass	Mobilization and strengthening exercises

Score	*Orientation*
5	What is the (year) (season) (date) (month) (day of week)?
5	Where are we (state) (country) (town/city) (hospital) (floor)?
	Registration
3	Repeat three words, for example, "ball," "flag," "tree."
	Ask the patient all three after you have said them. Give one point for each correct answer.
	Attention and Calculation
5	Begin with 100 and count backwards by 7 (stop after five answers). Alternatively, spell "world" backwards.
	Recall
3	Aak for three words repeated above. Give one point for each correct answer.
	Language
2	Show a pencil and a watch and ask subject to name them.
1	Repeat the following: "No ifs, ands, or buts."
3	A three stage command, "Take a paper in your right hand; fold it in half and put it on the floor."
	Read and obey the following: (Show subject the written item).
1	CLOSE YOUR EYES
1	Write a sentence
1	Copy a design



Total score possible = 30

Figure 21.E1 The mini-mental status examination is used to assess cognition during critical illness or delirium. *(Adapted from Folstein MF, Folstein SE, McHugh PR: "Mini-mental state": A practical guide for grading the cognitive state of patients for the clinician. J Psychiatric Res 12:189-198, 1975.)*

TABLE 21.4A ■ **General Criteria That Indicate Patient Is Not Ready to Initiate a Rehabilitation Session**

Heart Rate	***Pulse Oximetry/SpO_2***
> 70% age predicted maximal heart rate	< 88%
< 40 beats/minute; > 130 beats/minute	
New onset arrhythmia	
New anti-arrhythmia medication	
New MI by ECG or cardiac enzymes	
Blood Pressure	***Mechanical Ventilation (MV)***
SBP > 180 mm Hg	F_{IO_2} ≥ 0.60
MAP < 65 mm Hg; > 110 mm Hg	PEEP ≥ 10 cm H_2O
Continuous IV infusion of vasoactive medication (vasopressor or antihypertensive)	Patient-ventilator asynchrony
	Recent MV mode change to assist-control or pressure support
New vasopressor or escalating dose of vasopressor medication	Tenuous artificial airway
Respiratory Rate and Symptoms	***Alertness/Agitation and Cooperation***
< 5 breaths/minute; > 40 breaths/minute	Patient sedation or coma (RASS = –3, –4, or –5) (see Table 5.1 in Chapter 5 for RASS scale)
Patient feels intolerable DOE	Patient agitation requiring addition or escalation of sedative medication (RASS > 2)
	Patient refusal

DOE, dyspnea on exertion.

TABLE 21.4B ■ **General Criteria for Terminating a Patient's Rehabilitation Session**

Changes in Heart Rate	***Changes in Pulse Oximetry/SpO_2***
> 70% age predicted maximal heart rate	Decrease > 4%
> 20% decrease from resting heart rate	< 88%–90%
< 40 beats/minute; > 130 beats/minute	
New arrhythmia	
Changes in Blood Pressure	***Changes in Respiratory Rate and Symptoms***
SBP > 180 mm Hg	> 40 breaths/minute
> 20% decrease in SPB/DBP	Patient feels intolerable dyspnea
Orthostatic hypotension with presyncopal symptoms	

BP, blood pressure; DOE, dyspnea on exertion; ECG, electrocardiogram; F_{IO_2}, fraction of inspired oxygen; IV, intravenous; MAP, mean arterial blood pressure; MI, myocardial infarction; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; RASS, Richmond Agitation and Sedation Scale. *Maximal heart rate = 220 - age SBP/DBP, systolic/diastolic blood pressure; SpO_2, saturation of arterial oxygen by pulse oximetry.

Rancho Level of Cognitive Functioning Scale (RLCFS) used after traumatic brain injury (TBI)—are available to the rehabilitation specialists for a more focused screening. The RLCFS is an evaluation tool that identifies patterns of recovery in TBI patients with cognitive deficits in the first year postinjury. For patients who are not fully oriented, the orientation log (O-Log) is a quick 10-item scale that can be used during morning rounds to track orientation. This tool has been used in patients with brain injury, stroke, tumors, infections, and degenerative diseases. Patients who are oriented and score well on the O-Log can be progressed to the cognitive log (Cog-Log), a brief,

bedside measure of cognition. These tools do not replace more detailed testing but rather serve as simple and quick measurements that can be tracked over time.

For mechanically ventilated patients, in whom cognitive evaluation is more challenging, the confusion assessment method for the ICU (CAM-ICU) is a useful tool for the diagnosis of delirium (see Table 37.2 in Chapter 37). In general, the rehabilitation team also provides detailed and practical information regarding cognition, particularly as the functional abilities of the patient are impacted by cognitive impairments. For example, therapists who are teaching out-of-bed patients transfers may discover impaired motor planning, decreased attention, impaired memory, and decreased safety awareness. These factors will impact the patient's functional recovery and discharge plan.

AGITATION

Along with cognitive dysfunction, critically ill patients can exhibit neurobehavioral disturbances. Agitation in the critically ill patient can interfere with lifesaving treatment. It can elevate blood and intracranial pressure, jeopardize placement of intravenous (IV) lines, feeding tubes, endotracheal tubes, and bladder catheters. Because it can be disruptive, practitioners may be quick to control the behavior with medication. A brief assessment, however, may result in a more effective and precise treatment plan.

First, the target behavior should be identified specifically, for example, motor restlessness possibly resulting in falls or removal of lines or tubes. Next, any precipitating environmental factors should be identified and eliminated if possible, for example, overstimulation from multiple people talking at the bedside at once or procedures being performed without sufficient forewarning. Medical precipitants should also be considered and addressed, such as seizures, new medications, metabolic abnormalities, infection, sleep deprivation, and pain. The goals of treating agitated behavior are to maintain the safety of the patient, staff, visitors, and other patients and to decrease the intensity, frequency, and duration of episodes. Response to treatment can be measured objectively using the Agitated Behavior Scale (ABS), a 14-point scale (see Table 21.E3). Similarly, the Richmond Agitation and Sedation Scale (RASS) was developed to assess sedation and agitation in ICU patients and can be used to titrate sedating medication (see Table 5.1 in Chapter 5).

Antipsychotic medications are most commonly used for agitation or aggression. Although these are appropriate when the target behavior exhibits psychotic features, it is the sedating side effects rather than the antipsychotic features of these medications that are being exploited. Side effects with typical antipsychotics, such as haloperidol, include hypotension, sedation, confusion, dystonia, akathisia, lowering seizure threshold, and neuroleptic malignant syndrome. For patients with brain injuries, these side effects may occur more often. Haloperidol has also been implicated in delayed neuronal recovery and prolonged posttraumatic amnesia after brain injury. Given this information, some clinicians prefer using an atypical antipsychotic. At doses typically used, the incidence of extrapyramidal side effects is less than with the typical antipsychotics.

Benzodiazepines are also used to treat agitation. Again, it is the sedating properties of these medications that are exploited to control the behavior. Although unusual, benzodiazepines can cause a paradoxical increase in agitated behavior in some patients. Benzodiazepines can reduce respiratory drive and may exacerbate memory dysfunction and contribute to coordination and balance deficits. Other classes of medications have also been used to successfully treat agitation and aggression, including anticonvulsants such as valproic acid, carbamazepine, and gabapentin, antidepressants such as amitriptyline, and other serotonergic drugs as well as beta-blockers such as propranolol. However, when it is important to control target behavior quickly, despite lack of good comparative effectiveness studies, antipsychotic agents are likely more useful.

As a last resort, to prevent agitated behavior from interfering with lifesaving therapies, physical restraints may be necessary. This increases the degree of immobility and, consequently, its untoward

TABLE 21.E3 ■ **Agitated Behavior Scale (ABS)**

Patient_____ Period of Observation: a.m.

Observ. Environ._____a.m. From:_p.m.__/__/__

Rater/Disc._____ To:_p.m.__/__/__

At the end of the observation period, indicate whether the behavior described in each item was present and, if so, to what degree: slight, moderate, or extreme. Use the following numerical values and criteria for your ratings.

1 = absent: the behavior is not present

2 = present to a slight degree: the behavior is present but does not prevent the conduct of other, contextually appropriate behavior (the individual may redirect spontaneously, or the continuation of the agitated behavior does not disrupt appropriate behavior)

3 = present to a moderate degree: the individual needs to be redirected from an agitated to an appropriate behavior, but benefits from such cueing

4 = present to an extreme degree: the individual is not able to engage in appropriate behavior because of the interference of the agitated behavior, even when external cueing or redirection is provided

Do not leave blanks.

_____ 1. Short attention span, easy distractibility, inability to concentrate.

_____ 2. Impulsive, impatient, low tolerance for pain or frustration.

_____ 3. Uncooperative, resistant to care, demanding.

_____ 4. Violent or threatening violence toward people or property.

_____ 5. Explosive or unpredictable anger.

_____ 6. Rocking, rubbing, moaning, or other self-stimulating behavior.

_____ 7. Pulling at tubes, restraints, and so on.

_____ 8. Wandering from treatment areas.

_____ 9. Restlessness, pacing, excessive movement.

_____ 10. Repetitive behaviors, motor or verbal.

_____ 11. Rapid, loud, or excessive talking.

_____ 12. Sudden changes of mood.

_____ 13. Easily initiated or excessive crying or laughter.

_____ 14. Self-abusiveness, physical or verbal.

_____ **Total Score**

effects. For that and other reasons, it is important to exhaust all other measures before using physical restraints.

DYSPHAGIA, DYSPHONIA, AND APHASIA

Dysphagia and dysphonia are closely linked to functional restoration and are discussed in depth in Chapter 22. Additionally, many ICU patients with neurologic disorders may experience communication deficits, and speech language pathologists serve an important role in their recovery. For example, the speech therapist can suggest to other members of the rehabilitation team, ICU staff, and family, specific communication strategies to enhance comprehension and speech production. Strategies include directly addressing the patient using grammatically simple language, expressing one idea at a time, embellishing verbal inputs with visual or tactile cues to enhance comprehension, and facilitating nonvocal communication approaches, such as writing, drawing, and gesturing (Table 22.4 in Chapter 22).

CONTRACTURES AND SPASTICITY

Contractures are deformities characterized by decreased range of motion and caused by changes in various tissue types as a result of immobilization, inflammation, and spasticity. Contractures often perpetuate impaired mobility, pain, and the development of pressure wounds. Frequent repositioning, range-of-motion exercises, active mobilization, and the judicious use of splints are standard methods of contracture prevention. Additionally, positioning may alter the disuse atrophy associated with bed rest. Evidence suggests that immobilization in shortened positions enhances atrophy, whereas immobilization in lengthened and stretched positions may attenuate the loss of muscle fiber proteins. This has important clinical considerations for patients who are diagnosed with an orthopedic or neuromuscular condition limiting active movements of the extremities, or for patients who are medically paralyzed or require excessive sedation.

Spasticity is defined as rate-related resistance to passive limb stretch and occurs as part of the upper motor neuron syndrome in patients with brain and spinal cord injuries. Injury to the upper motor neuron pathways results in lack of descending inhibition to the muscle stretch reflex resulting in hyperexcitability. Tools, such as the Modified Ashworth Scale (see Table 21.E4), are used to measure spasticity. It is possible for spasticity to serve a useful purpose, giving patients a mechanism to "cheat" their lack of voluntary motor control. On the other hand, suboptimal treatment of severe spasticity can result in pain, contractures, skin breakdown, and even fractures and dislocations. Occasionally, sudden worsening of spasticity may be related to new pathologic process such as infection, fecal impaction, or some other noxious stimulus.

Aside from treating such aggravating factors, several systemic drugs are available to treat spasticity, including baclofen, tizanidine, dantrolene sodium, and diazepam. The primary dose-limiting effects of these medications are weakness and sedation. When prescribing these, it is helpful to define the goal of treatment. For example, in cases of severe adductor spasm of the lower extremities, goals would include improving access to the perineal area for hygiene, reducing pain, and improving out-of-bed transfers. Nonpharmacologic means are available to treat spasticity and contractures, including manual therapy techniques (stretching, joint mobilization), dynamic and static splints, and serial casting.

For brain-injured patients, dantrolene sodium, a sarcoplasmic reticulum calcium blocker, is often the antispasticity agent of choice since it is less sedating because of its peripheral site of action. Liver function tests should be ordered before initiating dantrolene therapy, which can produce hepatitis.

For spinal cord–injured patients, baclofen, an analogue of gamma-aminobutyric acid (GABA), is often the preferred first agent. High doses of baclofen may produce sedation, whereas rapid

TABLE 21.E4 ■ **The Modified Ashworth Scale of Muscle Spasticity**

0. No increase in muscle tone.
1. Slight increase in tone with a catch and release or minimal resistance at end of range.
2. Same as #2 but with minimal resistance through range following catch.
3. More marked increase in tone through range of motion.
4. Considerable increase in tone, passive movement difficult.
5. Affected part rigid

tapering can precipitate a withdrawal syndrome. Baclofen can also be administered by continuous intrathecal infusion, which avoids the dose-limiting effects mentioned earlier. Implanted intrathecal baclofen pumps are used in carefully selected patients with severe, generalized spasticity. Typically, this is a treatment option for patients with more chronic spasticity, although isolated case reports exist of its use acutely in brain-injured patients with autonomic dysregulation and dystonic posturing.

Temporary use of a short-acting parenteral benzodiazepine, such as diazepam, could be considered for patients without oral or enteral access. In this case, sedation or disinhibition may become limiting.

When systemic medications produce undesirable side effects, or when muscle overactivity is confined to a focal area, chemodenervation with ethyl alcohol, phenol, or onabotulinum toxin is a treatment option. Many physiatrists are knowledgeable in these procedures as are some neurologists.

AUTONOMIC IMBALANCES

Several types of autonomic imbalances can occur in the critically ill patient. These often present challenges with regard to mobilizing patients. Most commonly, as a result of deconditioning and sometimes neurologic injury, orthostatic hypotension is observed, an obvious challenge in transitioning from bedrest.

Autonomic dysreflexia occurs in cervical or high thoracic spinal cord injury and represents a manifestation of the disinhibited, autonomously functioning spinal cord distal to the lesion. Any sensory stimulus (usually noxious) to the disconnected spinal cord may result in a sympathetic autonomic response and vasoconstriction resulting in severe hypertension. Common triggers include urinary retention, constipation, nephrolithiasis, deep venous thrombosis, pressure ulcers, acute abdominal infections, and skin infections, including ingrown toenails. Treatment consists of eliminating the offending "noxious" stimulus. Immediate interventions should include sitting the patient up and establishing urinary outlet patency while continuing to search for other offending stimuli. Short-acting medications are used to control severe hypertension while the trigger is sought.

This population can also experience poikilothermia or temperature dysregulation, where temperature can be related to environmental temperature. Patients with acquired brain injuries can experience paroxysmal autonomic instability, a phenomenon that not only can prompt extensive medical workups but can also be associated with dystonic posturing severely affecting joint mobility. Although a detailed discussion of these autonomic imbalances is beyond the scope of this chapter, the rehabilitation team possesses a variety of skills and strategies to promote patient safety and functional recovery.

Planning for Rehabilitation after Leaving the Intensive Care Unit

The long-term goal of rehabilitation in the ICU is to develop a well-organized, comprehensive, and properly timed plan for when the patient leaves the ICU and the hospital. Such a plan should be based on the patient's physiologic status, psychosocial situation, and chronic care needs as well as prognosis for functional rehabilitation.

ICU-acquired problems, including neuromuscular weakness, loss of cardiopulmonary fitness, cognitive dysfunction, and malnutrition, influence functional recovery. The critically ill patient's response to therapeutic rehabilitation interventions is an important factor used to predict post-ICU care needs. For example, the greater the duration of bed rest, the greater the deconditioning response. Patients may demonstrate persistent tachycardia, tachypnea, and dyspnea during sitting and standing trials or demonstrate poor tolerance with low-level self-care activity indicating that

postacute rehabilitation at an inpatient rehabilitation facility (IRF) may be too demanding (they generally require the patient be able to do at least 3 hours of physical therapy per day).

Additionally, specific prognostic indicators define the natural history of some diseases. For example, loss of consciousness, posttraumatic amnesia, and anosognosia after traumatic brain injury forewarn of incomplete functional recovery and long-term rehabilitation and personal care needs after hospitalization. Rehabilitation delivery in the ICU is often overshadowed by patient care requirements for comfort and pain management, hemodynamic monitoring, fluid and electrolyte maintenance, medication administration, nutrition, wound care, as well as emotional and psychological support. Nonetheless, rehabilitation services should not be withheld from patients with severe physiologic impairments or poor prognostic indicators. Rather, rehabilitation is important for these individuals to minimize deconditioning, educate future care providers, optimally modify the patient's environment, and plan for ongoing rehabilitation from the ICU to the postacute care setting (see Figures 21.E2 and 21.E3). Rehabilitation interventions that are initiated early are feasible and safe and can be performed cost effectively.

POST-ACUTE CARE CONTINUUM

Traditionally, patients would transition from the ICU to a step-down or intermediate unit and then to a general nursing unit prior to leaving the acute care hospital. The environment has changed now, such that many patients leave the ICU directly. For patients who have functional deficits and require ongoing medical and nursing care prior to returning to the community, several different postacute settings can provide ongoing medical care or rehabilitation. The rehabilitation team attempts to accurately match the needs of the patients and social support network with the capability of the facility so that maximized functional independence, medical care, and appropriate payment follow.

Most geographic areas are served by varied levels of rehabilitative care: hospital-based (inpatient rehabilitation facility (IRF)/acute rehabilitation), skilled nursing facility (SNF), long-term acute care hospitals (LTACHs, see Chapter 109), home care, and outpatient rehabilitation services. These care settings are defined by Medicare, and other insurance systems often subscribe to Medicare guidelines. Critically ill patients may move through several care settings during their recovery.

Many patients are treated in inpatient rehabilitation facilities (IRF), also termed *acute rehabilitation*, after hospitalization. These facilities must meet criteria set by Medicare in order to maintain their status as IRFs. As a part of these criteria, patients must be able to perform three hours of therapy daily; they must require 24-hour rehabilitative nursing and have enough medical needs that require physician oversight of care. Achievable goals in terms of functional mobility and self-care must be present. These facilities are also required to maintain an interdisciplinary treatment approach. Admission to inpatient rehabilitation facilities is also limited to certain diagnoses, which are currently being disputed on the basis that these criteria are too arbitrary and result in diminished access to care.

Skilled nursing facilities (SNFs) are also defined by criteria for Medicare reimbursement for "skilled nursing care." Patients in these facilities must demonstrate a need for skilled care; this can be rehabilitation treatments or other skilled needs (e.g., complex wound care, IV and intramuscular injections, insertion of urinary catheters, and management requiring ongoing assessment). The care of every patient is under supervision of a physician, and physicians are available for emergencies. Nursing services must be available 24 hours a day. By definition, the amount of rehabilitation services that patients receive in SNFs varies. The term *subacute rehabilitation* is also sometimes used to denote an SNF with a focus on rehabilitation, although this is not an officially defined term.

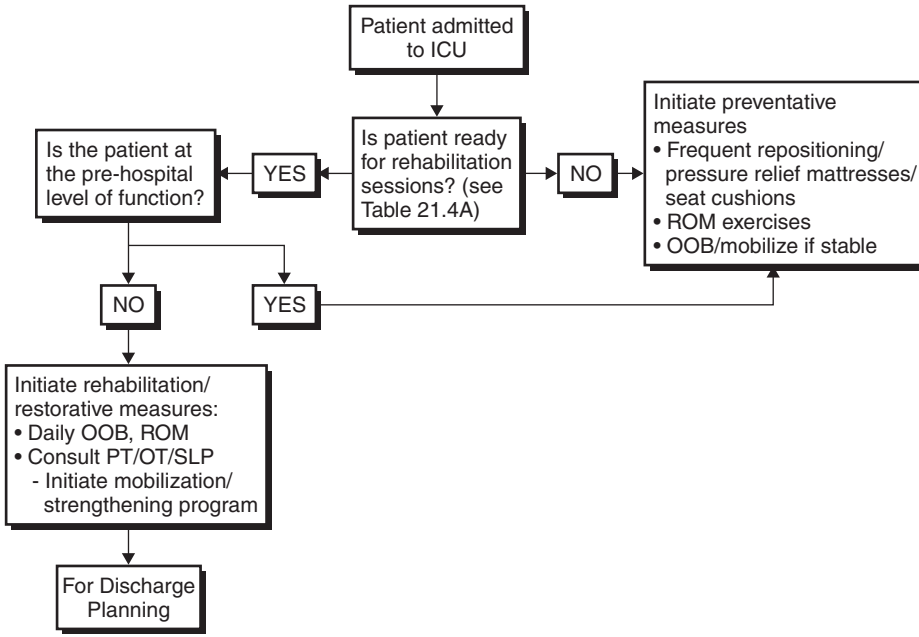


Figure 21.E2 Schematic flow diagram that indicates appropriate timing and level of rehabilitation activity for patients admitted to the intensive care unit. OOB, out of bed; OT, occupational therapy; PT, physical therapy; ROM, range of motion; SLP, speech language pathology therapy.

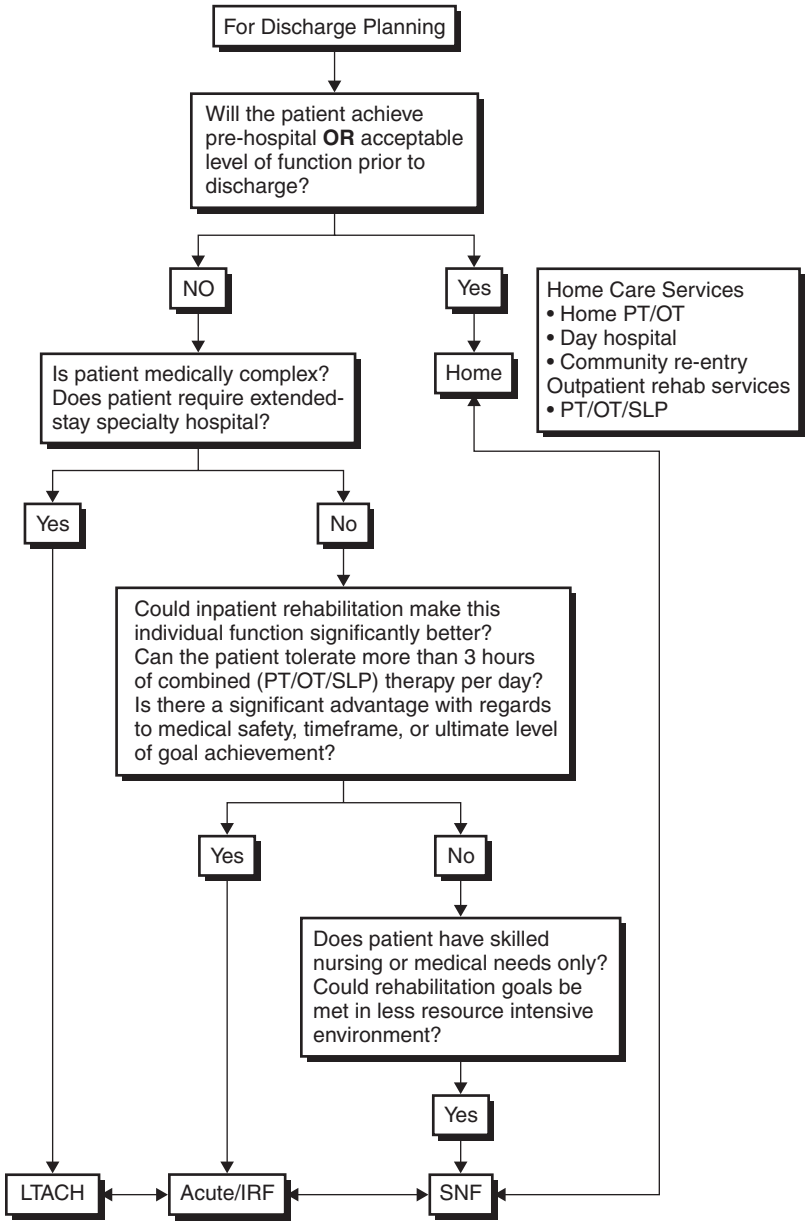


Figure 21.E3 Schematic flow diagram that indicates appropriate timing and level of rehabilitation activity for discharge planning purposes of patients being discharged from the intensive care unit. IRF, inpatient rehabilitation facility; LTACH, long-term acute care hospital; OT, occupational therapy; PT, physical therapy; SLP, speech language pathology therapy; SNF, skilled nursing facility.

Long-term acute care hospitals (LTACHs [see Chapter 109]) provide extended, intensive medical care to patients who are clinically complex, suffering from multiple acute or chronic conditions, and require resource-intensive care that cannot be provided in SNFs or nursing homes. The average length of stay is 25 days or more, and patients are often dependent on life support systems such as parenteral nutrition, respiratory and cardiac monitoring, dialysis, and mechanical ventilation.

Home care, or domiciliary care, comprises a range of services including those of professional health care providers (e.g., nurses; physical, occupational, and speech therapists; medical social workers; nutritionists) and life assistance services (e.g., home health aides, Meals On Wheels). These services are provided at home to recovering patients who are in need of medical, nursing, infusion, and pharmacy services as well as social and rehabilitation interventions. Patients must be homebound (where leaving the home requires great effort or the patient is unable to leave the home unassisted), have a physician's order, and have insurance authorization to be eligible for home health services.

As patients' mobility, activities of daily living (ADLs) performance, and safety improve, outpatient rehabilitation programs may meet the needs of those requiring ongoing physical, occupational, and speech therapies. Patients may have physical limitations but can safely travel to receive care. Outpatient rehabilitation services focus on optimizing the functional status of each patient within the home and community and facilitate a return to usual roles and responsibilities including household management, work, or leisure pursuits. In addition to the customary rehabilitation services, outpatient services include specialized programs such as day treatment and balance centers, driving rehabilitation, aquatic therapy, vocational rehabilitation, and community reentry programs.

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CHAPTER 22

Swallowing and Communication Disorders

Natasha Mirza ■ Andrew N. Goldberg ■ Melissa A. Simonian

The goal and challenge in treating intensive care unit (ICU) patients with communication and swallowing disorders are to restore two basic human functions: speaking and eating. Verbal communication and normal swallowing function can be compromised in ICU patients not only by disorders causing critical illness but also by many of the ICU treatments. For example, all patients with prolonged mechanical ventilation or tracheostomy are at increased risk for speech and swallowing problems. The prognosis for restoring normal speech and swallowing can be improved if one applies a multidisciplinary intervention strategy early in the course of the patient's recovery from critical illness. Three major objectives of this strategy are to establish appropriate alternative methods of communication, to prevent aspiration, and to provide oral nutrition. The consequences of dysphagia in noncritically ill patients who are recovering from critical illness or injury but are neurologically impaired include aspiration, pneumonia, malnutrition, placement of feeding tubes, decreased quality of life, increased institutional care, and increased mortality risk.

Approach to Swallowing Dysfunction in the Intensive Care Unit Patient

A swallowing assessment should be made on all ICU patients as they recover from critical illness. Problems with swallowing (*dysphagia)* place patients at high risk for aspiration (defined as penetration of any material below the vocal cords) when they resume oral feeding and drinking. Dysfunction of the normal swallowing mechanism should be suspected in patients after neurologic events or surgical procedures that might affect function of the pharynx or larynx. The same suspicion should apply to all patients who have undergone tracheotomies, who have had prolonged translaryngeal intubation, or both. Similarly, one should assume that patients with endotracheal tubes in place cannot swallow food safely, and attempts at oral feeding should wait until after extubation or conversion to tracheostomy with spontaneous breathing. Consultation with an otolaryngologist, a speech-language pathologist, or both may be indicated for these ICU patients before restarting oral fluids or feeding.

The Swallowing Mechanism

Deglutition is the act of swallowing in which a food or liquid bolus is transported from the mouth through the pharynx and esophagus into the stomach. The anatomic areas involved in swallowing include the oral cavity, pharynx, larynx, and esophagus. Normal deglutition involves a complex series of voluntary and involuntary neuromuscular contractions proceeding from the mouth to the stomach and is commonly divided into three sequential phases (Table 22.1). During the *oral phase*, intact labial muscles are necessary to ensure an adequate seal that prevents leakage from the oral cavity. This is followed by contractions of the tongue and striated muscles of mastication. The muscles work in a coordinated fashion to mix the food bolus with saliva and propel it from

TABLE 22.1 ■ **Three Phases of Normal Swallowing**

Phase	Description
Oral phase	The food bolus is manipulated, masticated, formed, and propelled posteriorly by lingual and buccal movements
Pharyngeal phase	The swallow reflex is triggered and the airway is closed
	As the food bolus moves through the pharynx, the upper esophageal sphincter relaxes
Esophageal phase	Esophageal peristalsis carries the bolus through the cervical and thoracic esophagus into the stomach

TABLE 22.2 ■ **Actions of the Swallow Reflex**

Action 1	Elevation and retraction of the soft palate, with complete closure of the velopharyngeal port to prevent material entering the nasal cavity
Action 2	Initiation of pharyngeal peristalsis to carry the bolus through the pharynx
Action 3	Elevation of the larynx and its closure by the epiglottis to prevent food or fluid from entering the trachea
Action 4	Relaxation of the upper esophageal sphincter (cricopharyngeus), allowing the food bolus to pass into the esophagus

the anterior oral cavity into the oropharynx, where the involuntary swallowing reflex is triggered. The posterior brain controls output for the motor nuclei of cranial nerves V, VII, and XII, and the entire sequence lasts about 1 second.

The *pharyngeal phase* begins with triggering of the swallow reflex. This reflex comprises a series of coordinated movements crucial to successful swallowing (Table 22.2). In the posterior oropharynx, a complex and precisely coordinated succession of muscular contractions and relaxations occurs. The soft palate elevates to close the nasopharynx, and the suprahyoid muscles pull the larynx up and forward. The epiglottis moves downward to cover the laryngeal opening while striated pharyngeal muscles contract to move the food bolus past the cricopharyngeus muscle (the physiologic upper esophageal sphincter) and into the proximal esophagus. This swallowing reflex also lasts approximately 1 second and involves the motor and sensory tracts from cranial nerves IX and X.

The *esophageal phase* begins when the upper esophageal sphincter relaxes. This allows the peristaltic wave (which began in the pharynx with triggering of the swallow reflex) to continue in sequential fashion down the esophagus into the stomach. As food is propelled from the pharynx into the esophagus, involuntary contractions of the skeletal muscles of the upper esophagus force the bolus through the mid and distal esophagus. The medulla controls this involuntary swallowing reflex, although voluntary swallowing may be initiated by the cerebral cortex. The lower esophageal sphincter relaxes at the initiation of the swallow, and this relaxation persists until the food bolus is propelled into the stomach. It may take 8 to 20 seconds for the contractions to drive the bolus into the stomach.

Clinical Assessment for Swallowing Dysfunction

Patients who have dysphagia may present with a variety of complaints, but they usually report coughing or choking with or without eating. The presence of a tracheostomy tube often contributes to aspiration and swallowing dysfunction, and a swallowing assessment is often difficult in

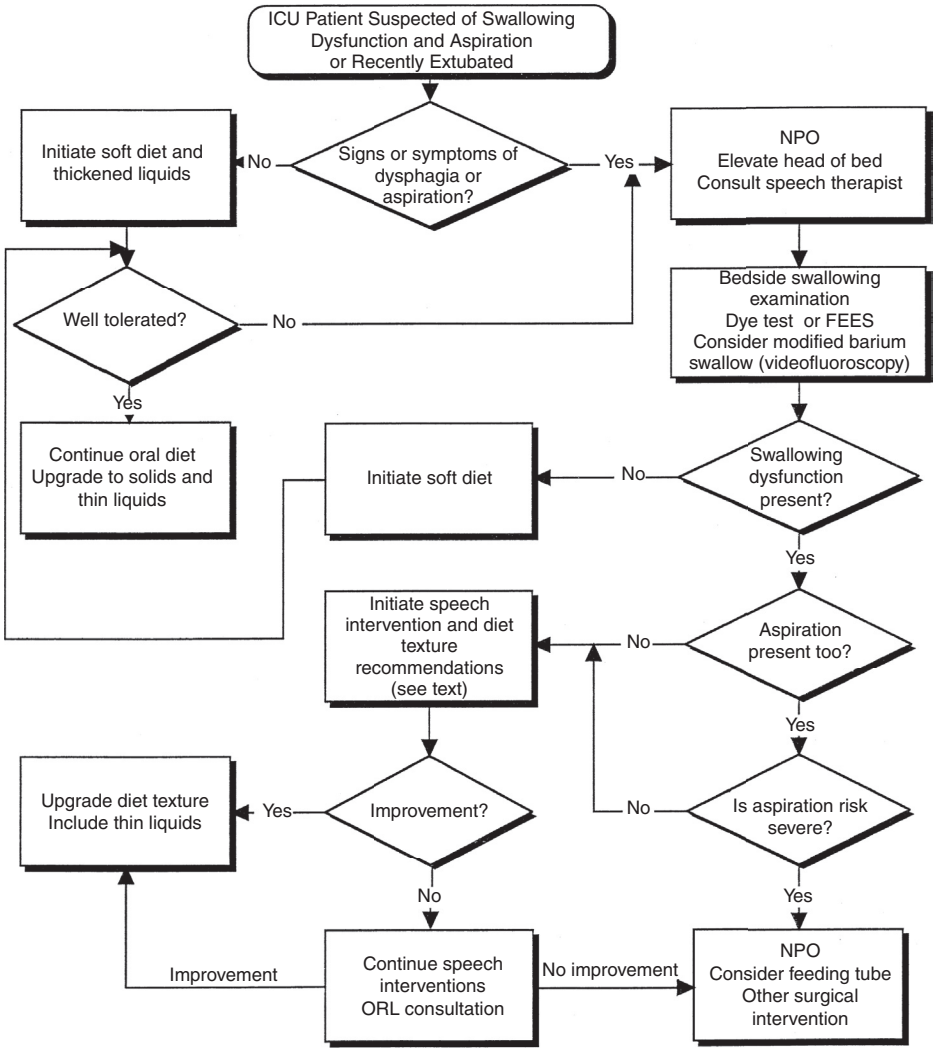


Figure 22.1 Flow diagram illustrating the general approach to ICU patients suspected of having swallowing dysfunction (see text for details). FEES, fiberoptic endoscopic evaluation of swallowing; NPO, nothing by mouth; ORL, otorhinolaryngology.

these circumstances. A swallowing evaluation starts with a review of the patient's medical and surgical history, hospital course, and respiratory and nutritional status (Figure 22.1). A cognitive screening and complete oral physical examination should then be performed. Patients who are not alert or who are severely cognitively impaired may not be candidates for undergoing further bedside tests to evaluate the risk of aspiration. Oxygen desaturation and copious secretions are also contraindications to these tests.

Patients with *oropharyngeal dysphagia* present with difficulty in initiating swallowing and may also have associated coughing, choking, or nasal regurgitation. The patient's speech quality may have a nasal tone. These dysphagias are most often associated with neurologic conditions like a stroke. Visualizing the structural integrity of the oral cavity, the presence or absence of teeth, and

the movement and coordination of the tongue, lips, mandible, and palate as well as the status of the mucosa and hydration of the tissues provides the clinician with information regarding the oral phase of the swallow as well as speech intelligibility. Drooling is a sign of poor oral control. Certain medications, especially psychotropic medications, induce xerostomia and thereby prevent adequate mixing and propulsion of the food bolus into the posterior oropharynx. Patients with *esophageal dysphagia* present with the sensation of food sticking in their throat or chest. However, the patient's description of the perceived location of the obstruction often does not correlate well with actual pathology, especially if the perceived location is in the cervical area.

BEDSIDE EVALUATION OF SWALLOWING

Assessment of the oral phase of the swallow involves determining the patient's ability to masticate, control, propel, and clear a food bolus from the mouth without a delay. Assessment of the pharyngeal phase of the swallow includes observing laryngeal elevation and noting changes in vocal quality and an associated cough or throat clearing. Gurgling with speech or clearing of the throat indicates the presence of secretions pooled near the larynx. Laryngeal elevation is observed by palpating the neck to feel the larynx move superiorly and anteriorly during the swallow (Table 22.3). Observing the patient swallowing a variety of liquids and solids can be helpful. The patient should demonstrate enough neuromuscular control to chew food, mix it into a bolus with saliva, and propel it to the posterior pharynx without choking or coughing. Elevation of the larynx during the swallowing reflex protects the airway and opens the upper esophageal sphincter. Normal laryngeal ascent can be palpated by placing the index finger above the patient's thyroid cartilage when the patient swallows. The cartilage should move cephalad against the physician's finger.

Assessment of the esophageal phase of the swallow cannot be performed at the bedside. Dyed food is administered while the patient is observed for manifestations of aspiration—for example, coughing or vocal quality changes. These may indicate delayed aspiration, and the patient should be encouraged to cough and clear the airway. If the ICU patient has a tracheostomy, the lower airway can be easily accessed via suctioning. Dyed food or fluid ingested by the patient that is subsequently deep suctioned or expectorated via the tracheostomy tube is clear evidence of aspiration.

If no aspiration is evident with the first swallowing attempts, the test continues with successive swallows of varied consistency and size of boluses. If the patient aspirates, one must decide whether to proceed or discontinue the examination. This decision rests on the patient's ability to cough and clear the material and overall respiratory condition. The patient's respiratory status should be monitored over the next 24 hours to note the presence of any additional dyed material at the tracheostomy site. Because patients may aspirate intermittently, aspirate only certain consistencies of material, or aspirate silently without overt clinical signs, a close monitoring of the tracheal aspirate is necessary.

Videofluoroscopy

A videofluoroscopic swallowing evaluation (modified barium swallow) is a dynamic assessment of swallowing. It is performed by a team composed of a radiologist and a speech pathologist with

TABLE 22.3 ■ **Overt and Covert Signs of Aspiration during Bedside Evaluation**

Overt Signs	Covert Signs
Buccal pocketing (food retention in the cheek pouch)	Lower lobe radiographic infiltrates
Coughing with oral intake	Increased pharyngeal secretions requiring transoral suctioning
Drooling	Recurrent aspiration pneumonia
"Wet" vocal quality after eating	Significant weight loss

expertise in swallowing disorders and is used as an adjunct to the clinical bedside evaluation and fiberoptic endoscopic evaluation of swallowing (FEES), described later. Videofluoroscopy allows observation of the dynamics of the oral, pharyngeal, and esophageal phases of swallowing and determination of the presence and mechanism of aspiration. This study is particularly important when intermittent aspiration occurs during feeding trials or if silent aspiration is suspected secondary to sensory level deficits. The patient has to be transported to the radiology suite for this study, which is often difficult in the ICU setting.

The evaluation usually begins with the administration of a thick liquid contrast bolus to swallow. This contrast provides an adequate coating of surfaces so that the structures can be well visualized. The patient should be positioned upright and encouraged to feed himself or herself, if possible. Active patient participation enables observation of the cognitive aspects that contribute to swallowing as well. If the patient tolerates a small initial bolus, larger boluses of varied consistencies are administered to stress the patient's swallowing ability.

The timing of aspiration during the swallow is important. Aspiration can occur before swallow initiation, amid the pharyngeal phase (midswallow), or after swallow completion by overflow of pooled or residual contrast material into the trachea. The timing and amount of aspiration determine which compensatory positioning maneuvers should be tried. Among these maneuvers are head turning, chin tuck, and the Valsalva maneuver. The effectiveness of each maneuver can be readily evaluated by repeated administration of contrast material.

The esophagus can also be visualized during this study, noting the presence of structural abnormalities, decreased peristaltic action, and reflux. The limitations of videofluoroscopy include radiation exposure, the need for examiner expertise, transport of the patient, and the taste of the contrast material.

A barium study assesses motility better than endoscopy and is relatively inexpensive with few complications. However, it can be difficult to perform in sick or uncooperative patients.

Double-contrast studies provide better visualization of esophageal mucosa. Fluoroscopy can also identify abnormalities in the mouth and oropharynx and, if observed closely, can provide some detail about function, detecting reflux and abnormal peristalsis. This evaluation uses quantifiable measures of swallows of a variety of bolus consistencies to help objectively identify the presence, nature, and severity of oropharyngeal swallowing problems and to assess treatment options.

FIBEROPTIC ENDOSCOPIC EVALUATION OF SWALLOWING (FEES)

In performing a fiberoptic endoscopic evaluation of swallowing (FEES), a flexible fiberoptic scope is inserted nasally and positioned to view the pharynx and larynx. Touching the mucosa helps assess laryngeal sensitivity and a cough reflex. Thickened liquids, thin liquids, and solids with a food dye are introduced, and the pharyngeal and laryngeal dynamics are examined for dysfunction. Patients who show aspiration without cough are at high risk of pulmonary complications. Compensatory maneuvers can be used such as head turning and chin tuck to determine if they improve the swallowing mechanism. Because it is a relatively simple examination that can be performed at the bedside and repeated as often as necessary without any risk of radiation exposure, it is of great value. Limitations of this test are that it does not provide a complete assessment of the oral cavity, bolus transit, or esophageal function. However, as speech pathologists are becoming more comfortable with this study, they are performing the test more frequently, in conjunction with an otolaryngologist or intensivist.

Management of Swallowing Dysfunction

Management aims to improve the swallowing function to achieve adequate nutrition and to eliminate aspiration. Treatment is goal directed, incorporating compensatory strategies, therapeutic

techniques, or surgical intervention in rare cases. The preferred initial management of patients with swallowing dysfunction who are at risk for aspiration is non-invasive. The majority of ICU patients can be managed in this way.

GENERAL APPROACHES

For patients at risk of aspiration, reflux and aspiration precautions should be implemented. These include a 30-to-45 degree elevation of the head of the bed, cessation of oral feeding, and placement of a cuffed tracheostomy tube in tracheostomized patients (Figure 22.2). Enteral or parenteral alimentation should be considered in any patient who cannot be fed orally (Chapter 15).

Intubated patients are at increased risk for aspiration. Even patients intubated for a few days may suffer from swallowing dysfunction after extubation. Although the cause of this dysfunction is not known, it is usually self-limited and, as a rule, a mechanical soft diet can be initiated in these patients without problems. Persistent dysfunction should be evaluated by a speech-language pathologist, an otorhinolaryngologist, or both. One of the possible explanations for this swallowing dysfunction after extubation is thought to be a combination of muscle "freezing" (attributable to nonuse while intubated) and loss of sensory reflexes. FEES in postextubation patients allows for a rapid evaluation of deglutition and for the immediate initiation of symptom-related rehabilitation or for an early resumption of oral feeding.

A speech pathologist or otorhinolaryngologist should be consulted to evaluate persistent dysfunction—that is, dysfunction that is still present 24 hours after extubation.

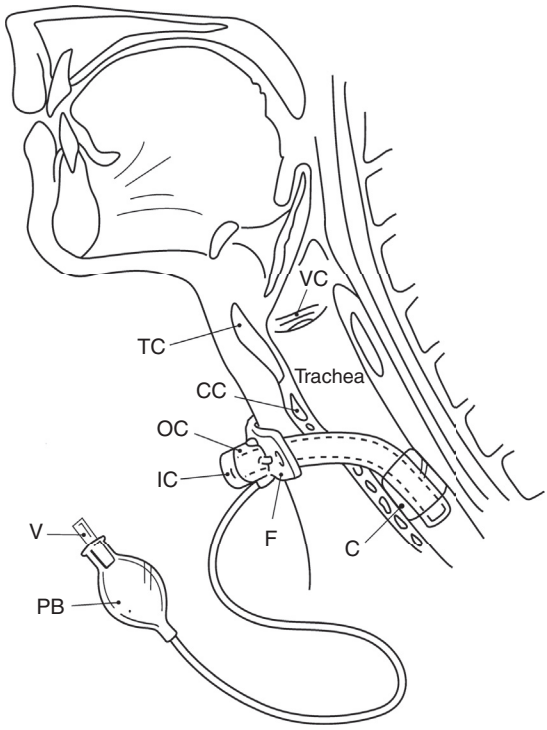


Figure 22.2 Sagittal midline view of trachea, larynx, and pharynx with an inflated cuffed tracheostomy tube in place. The tube enters the trachea via a surgical opening at the level of the second or third tracheal rings. C, cuff of tracheostomy tube (see Figure 22.3 for details); CC, cricoid cartilage; F, flange of tube; IC, inner cannula of tube (represented by dashed lines within the outer cannula); OC, outer cannula of tube; PB, pilot balloon; TC, thyroid cartilage; V, one-way valve; VC, vocal cords. *(Courtesy of Voicing, Inc., Newport Beach, CA.)*

NON-INVASIVE THERAPIES AND PROSTHETICS

For swallowing dysfunction, the initial treatment is non-invasive, either indirect or direct. Indirect treatments include exercises to increase oral motor control, thermal stimulation of the swallow reflex, and vocal exercises to increase adduction of the vocal cords, thereby improving airway protection. Direct interventions constitute modification of swallowing technique or the bolus texture. Because thin liquids are the most difficult to control, using thick liquids and pureed solids (pudding consistency) provides a helpful early intervention in cases of mild to moderate dysfunction. Modification of head or body position by sitting the patient upright and using a Valsalva maneuver ("supraglottic swallow") are other useful techniques for managing those with mild aspiration risks.

INVASIVE INTERVENTIONS

Failure of initial treatment with conservative measures occurs for a variety of reasons. They include severe neuromuscular dysfunction or cognitive deficits, anatomic obstruction by a scar band or tumor, and anatomic alteration by trauma or surgery. Surgical intervention may be used to provide an alternate route for alimentation, relieve a physical obstruction, or separate the air and food passages.

Tracheostomy and Feeding Tube Placement

In patients with refractory aspiration, the most common procedures employed are placement of a tracheostomy and feeding tube. There is some irony in this because a tracheostomy, as noted earlier, can actually increase one's risk of aspiration. Tracheostomy tubes do, however, provide a route for pulmonary toilet and suctioning of aspirated contents and the thick secretions characteristic of some of these patients.

Some patients benefit from inflation of the tracheostomy tube cuff, which assists in somewhat decreasing aspirated material from falling into the lower respiratory tract. Tracheostomy cuff pressures must be carefully monitored to prevent mucosal and cartilage ischemia, leading to necrosis and tracheal stenosis (Chapter 30). Balloon overinflation can also impede the flow of material down the esophagus by compression of the esophagus through the membranous posterior tracheal wall and should be avoided.

In other patients, the cuff may be left deflated or an uncuffed tube may be used. Placement of a Passy-Muir one-way "speaking valve" attached to the proximal adapter of the tracheostomy tube is often helpful in decreasing the risk of aspiration as the restoration of laryngeal airflow improves laryngeal function. It is also helpful in strengthening the patient's capacity to build up intratracheal pressure (before glottic opening), which is needed for producing an effective cough.

A gastrostomy feeding tube is helpful in allowing patients to achieve their caloric needs while decreasing the risk of aspiration from attempts at oral feedings (Chapters 15 and 16). However, in those who have problems with reflux or are at high risk of aspiration, a postpyloric nasoenteral or oral-enteral small bore feeding tube or a surgically placed jejunostomy (or a double lumen gastric-jejunostomy [G-J]) tube is preferred,. Subsequent oral feeding trials can be initiated in conjunction with a decrease in enteral/jejunostomy tube feedings until the patient is able to comfortably supply all his or her nutritional needs orally. In some cases, the combination of a tracheostomy and placement of a gastrostomy tube or jejunostomy tube can be performed under one anesthetic in the operating room.

Upper Esophageal Sphincterotomy

Selected patients with neuromuscular dysfunction or isolated cricopharyngeal achalasia may benefit from release of the cricopharyngeus muscle (upper esophageal sphincter). This procedure

carries little morbidity and can be performed selectively using local anesthesia if necessary. Its indications include a persistent, prominent, tight cricopharyngeus muscle in a patient without significant gastroesophageal reflux disease. In some of these patients with a very tight cricopharyngeus, a chemical myotomy with botulinum toxin can also be performed. However, botulinum toxin injections require electromyography for accurate placement, and that is logistically difficult in the ICU setting.

Verbal Communication Problems

Communication with ICU staff, family, and friends is vital for the patient's physical and psychological recovery. Adequate communication enables patients to participate in their care, which can decrease their feelings of insecurity and anxiety. In the ICU, impediments to verbal communication include the presence of an endotracheal or tracheostomy tube, abnormal function of the articulatory musculature, cognitive and other neurologic impairments, effects of sedatives and analgesics, and concurrent morbidities.

Most ICU patients are medically unstable and require flexible, functional, and practical interventions to improve their communication. In developing an effective nonverbal system of communication, the patient's family and ICU nurses, generally guided by a speech-language pathologist, should consider the patient's cognitive and physical abilities as well as the basic communication needs. Commercially available computer-assisted communication systems are expensive and inappropriate for short-term use. If the patient has a tracheostomy, a modification of the tracheostomy tube or placement of a one-way valve may facilitate verbal output. Various nonverbal (nonlaryngeal) and verbal (laryngeal) options are available to achieve effective communication (Table 22.4).

Tracheostomy Tubes

INDICATIONS AND INSERTION

A tracheostomy is commonly performed when there is a prolonged need for an artificial airway, when pulmonary toilet is needed, or when there is evidence of upper airway obstruction. Prospective studies have indicated that the main advantage in converting an endotracheal tube to a tracheostomy tube in ICU patients receiving mechanical ventilation is that the latter provides a more comfortable airway. It also provides a more secure airway for chronically ventilator-dependent patients being transferred to subacute or long-term acute or chronic care facilities. The irritation and inflammation at the level of the subglottis caused by a translaryngeal tube are

TABLE 22.4 ■ **Nonlaryngeal and Laryngeal Approaches to Promote Communication**

Nonlaryngeal Approaches	Laryngeal Approaches
Gestural, sign, eye gaze techniques	Fenestrated tracheostomy tubes
Picture, word, alphabet boards	Tracheostomy speaking valves (Passy-Muir valves)
Lip-speaking words	Controlled tidal volume leaks*
Alaryngeal devices (e.g., electrolarynx)	Talking tracheostomy tubes

*This method uses extra-large tidal volumes, a part of which is allowed to leak around a partially deflated cuff (of a tracheostomy tube or endotracheal tube) while the patient is on the assist-control mode of mechanical ventilation. If used, the patient must have constant bedside attendance by ICU staff to ensure that adequate tidal volumes are still being delivered to the lungs.

decreased, potentially reducing the long-term risk of a subglottic stenosis. These are the reasons for recommending conversion to a tracheostomy in a patient who is endotracheally intubated for more than 2 weeks.

A tracheostomy involves creating an opening in the trachea at the level of the second or third tracheal ring (see Figure 22.2). The tracheostomy tube is inserted to maintain an opening after the surgical procedure. The tube must be left in place during the initial healing process to allow the skin opening and tracheal opening to form a single epithelialized tract. The tube is generally changed after a minimum of 3 days if the need for a cuffed tube is no longer present and the patient needs a smaller tracheostomy tube. Tracheostomy tube changes earlier than 72 hours are not advised, as the tract may not be well formed. If the tracheostomy tube is inadvertently pulled out during this time, the skin and tracheal openings may become misaligned and result in potentially catastrophic loss of the airway and respiratory compromise.

COMPONENTS AND TYPES OF TRACHEOSTOMY TUBES

Standard tracheostomy tubes come in a variety of sizes and types, but most have similar parts (Figure 22.3 and Table 22.5). Tracheostomy tubes are made of silicone, plastic, or metal. When used for ICU patients on ventilators, they are commonly cuffed and nonfenestrated. Later, during recovery from critical illness, fenestrated or cuffless tracheostomy tubes may be used (see Figure 22.3).

A *cuffed* tracheostomy tube prevents air escape from the lower airway during mechanical ventilation. Having the cuff inflated also somewhat reduces the risk of aspirated material entering the trachea from the upper airway. Cuff pressures should be checked regularly at 8- to 12-hour intervals to avoid high cuff pressures that might cause ischemic injury to the tracheal mucosa. Because capillary pressures in tracheal mucosa are estimated at 20 to 25 mm Hg (27-34 cm H_2O), cuff pressures should be maintained at or below 25 mm Hg with the airway sealed. A cuffless tube is usually used during downsizing of a tracheostomy for decannulation or when the indication for continued ventilator support is no longer present.

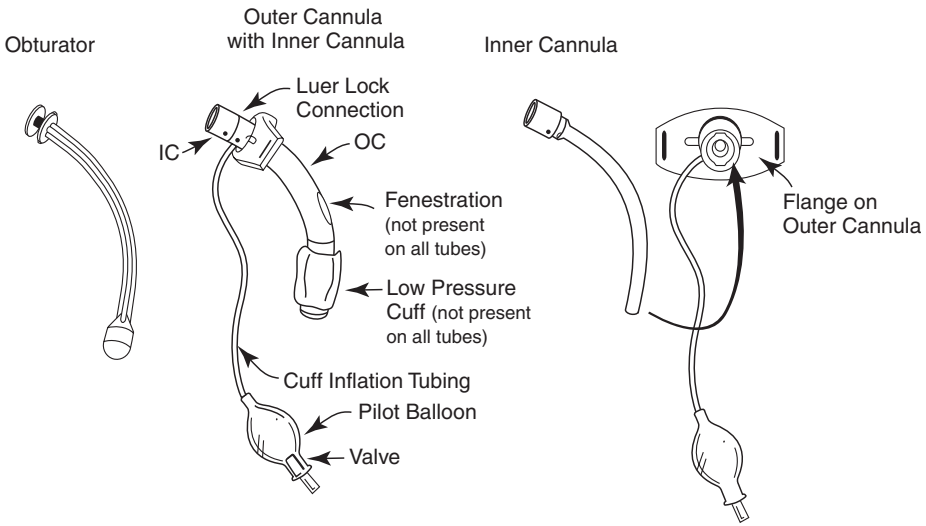


Figure 22.3 Components of cuffed tracheostomy tubes (see Table 22.5 and text for details of each part). IC, inner cannula; OC, outer cannula. *(Modified from Logemann JA: Evaluation and Treatment of Swallowing Disorders. San Diego: College Hill Press, 1983.)*

TABLE 22.5 ■ **Common Components of Tracheostomy Tubes**

Component	Description and Comment
Outer cannula	The outside structure of the tracheostomy tube that is inserted into, and remains in place in, the trachea; a flange attached to its proximal end is used to secure the tube to the neck with ties
Inner cannula	A fitting that slides inside the outer cannula and can be easily removed for cleaning; most are cleaned every 8 hours; some tubes do not use inner cannula, predisposing them to risk of occlusion from inspissated secretions
Obturator	A solid insert that is used to facilitate introduction of the outer cannula during replacement of tracheostomy tubes; it is removed immediately after the latter has been safely guided into the trachea
Cap (also called a plug, cork, or button)	A small, round piece of plastic that can be placed in the tracheostomy tube (in place of the inner cannula) to occlude the proximal opening; with occlusion of the tube, patients breathe around the tube translaryngeally and not through it

If cuff pressures higher than 25 mm Hg are needed to occlude the airway, then one should consider that the tube's diameter is too small for an anatomically normal trachea (e.g., using a cuffed 6 Shiley tracheostomy tube in a large male patient). In this situation, one should change to a larger diameter cuffed tube (e.g., change to a cuffed 7 or 8 Shiley tube). If there still is a need for high cuff pressures to occlude the airway, then one should consider misalignment of the distal end of the tube in the trachea so that the cuff is eccentric in its location. Another explanation is that the patient has developed tracheomalacia at the site of the inflated cuff. In the latter circumstance, one should not allow the cuff to be inflated > 25 mm Hg to seal the airway because this will eventually result in even more abnormal dilatation of the trachea at that site. Instead, one should consider changing the tube to a tracheostomy tube of the same size with elongation of the intratracheal portion (e.g., change a standard cuffed 8 Shiley tracheostomy tube to a cuffed distal XL 8 Shiley) that will result in moving the site of contact between the inflated cuff and inner trachea about 2 cm distally.

There are also extra-long tracheostomy tubes that have an elongated portion between the flange and the entrance through the tracheal stoma (see Figures 22.2 and 22.3). One example is the proximal XL Shiley. These are useful for placement in patients with increased thickness of the space between skin and tracheal opening (e.g., as a result of morbid obesity).

A *fenestrated* tracheostomy tube has a precut opening (window) in the posterior surface of the outer cannula (see Figure 22.3). The fenestration allows air to pass serially from the lungs, through the fenestration, through the vocal cords, and into the upper airway. They are used as adjuncts to breathing around a deflated cuff with the tube "capped" (i.e., placing an occluding plastic cover on the proximal end of the tube's inner cannula) in order to enlarge the passage for air movement. There is a risk of the fenestrations leading to tracheal wall irritation, and therefore an alternative to inserting a fenestrated tube is to change to the next smaller size nonfenestrated cuffed tube. This also offers a larger passageway for spontaneous breathing because its deflated cuff is much smaller than the larger tube's cuff. With occlusion of the tracheostomy tube and the cuff deflated, patients breathe around the tracheostomy tube and not through it. *Care must be taken to deflate the cuff (or use a cuffless tracheostomy tube) before capping to ensure the presence of an adequate breathing passageway around the tube.* The cap must be removed quickly if the patient experiences shortness of breath during a "capping" trial of breathing.

Fenestrated tubes generally should be avoided in patients who are at high risk for aspiration because secretions or food can easily pass through the fenestration into the airway. A fenestration may become occluded by being up against the tracheal wall or by the development of granulation

tissue induced by its irregular surface rubbing on the mucosa of the posterior trachea. Smaller tracheostomy tubes allow a patient to phonate, and improved communication in the ICU population leads to the improved mental health of these patients. Laryngeal airflow also improves upper airway sensation and can improve swallowing.

DECANNULATION

When the tracheostomy tube is no longer indicated, it should be removed. The patient's ability to breathe comfortably and capacity to handle respiratory secretions without aspiration are factors in the decision to decannulate a tracheostomy tube. Decannulation is generally appropriate when a patient has demonstrated the ability to tolerate sustained capping of the tracheostomy tube during day and night while asleep.

Decannulation can be accomplished by removing the tracheostomy tube and allowing the opening to close naturally. After the tube is removed, stomal closure generally occurs over a 4- to 7-day period with no additional intervention. Typically, progressively smaller tracheostomy tubes (downsizing) are used before final removal of all tubes. Capping and one-way speaking valves are used in the decannulation process as well as to facilitate swallowing, communication, and comfort.

Tracheostomy Tubes and Communication

As noted earlier, tracheostomy tubes (both fenestrated and nonfenestrated) with deflated cuffs allow air from the lower trachea to pass into the upper airway. By occluding the tracheostomy tube opening with a finger or otherwise, the patient can speak using his or her larynx. A *tracheostomy valve* is a one-way speaking valve—for example, a Passy-Muir tracheostomy speaking valve—that obviates the need for using one's finger to close the tracheostomy. It allows air to be inhaled easily through the tracheostomy tube and then closes with exhalation so that air can be expired only through the vocal cords and oral cavity, which allows phonation. However, not all patients with tracheostomies are appropriate for the use of a speaking valve. For example, the patient must be able to tolerate cuff deflation and be off mechanical ventilation at the time. The patient should have minimal secretions as well so that the valve does not become clogged after coughing. Some centers avoid the use of valves in patients with cuffed tubes because of the risk of placing a valve on an inflated tube and preventing the exhalation of air.

Talking tracheostomy tubes are designed to provide a means of verbal communication in the case of the chronically ventilator-dependent patient. Speech is produced from an independent air source flowing through a catheter that has a fenestration just *above* the tracheostomy tube cuff. These tubes provide airflow through the vocal folds, producing phonation while maintaining a closed ventilatory system. The tracheostomy cuff remains inflated with these tubes. The air port and the fenestration, however, can become clogged with secretions, affecting the vocal quality. Finally, patients must be able to synchronize their speech with the ventilator's inspirations.

Conclusion

Awareness of speech and swallowing impairments in ICU patients is paramount to the well-being of these critically ill patients, as it may lead to solutions that will allow them to eat and drink without the risk of aspiration and to communicate effectively with family, friends, and the ICU staff. Consultations with otolaryngologists, speech pathologists, or both early in the course of ICU hospitalizations can minimize morbidities associated with speech and swallowing problems in this population.

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Gomes Silva BN, Andriolo RB, Saconato H, et al: Early versus late tracheostomy for critically ill patients. Cochrane Database Syst Rev. 3:CD007271, doi:10.1002/14651858.CD007271.pub2 2012 Mar 14.

This recent review in the Cochrane Database of systematic reviews found updated evidence was of low quality and limited in number (only four studies); they found no advantage of tracheotomies in ICU patients done early (2 to 10 days after intubation) or late (> 10 days after intubation) in any subgroup characteristics.

Griffiths J, Barber VS, Morgan L, Young JD: Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation. BMJ 330(7502):1243, 2005 May 28. Epub 2005 May 18.

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Terzi N, Orlikowski D, Aegerter P, et al: Breathing–swallowing interaction in neuromuscular patients: a physiological evaluation. Am J Respir Crit Care Med 175:269-276, 2007.

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Tibbling L, Gustafsson B: Dysphagia and its consequences in the elderly. Dysphagia 6:200-202, 1991.

This investigation studied almost 800 elderly people and found that difficulty in swallowing led to physical and psychosocial problems for these individuals.

Trate DM, Parkman HP, Fisher RS: Dysphagia: evaluation, diagnosis, and treatment. Prim Care 23:417-432, 1996.

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CHAPTER 23

Care of the Patient Infected with Human Immunodeficiency Virus Infection

Ian Frank ■ Naasha Talati

Advances in antiretroviral therapy have transformed the lives of people living with human immunodeficiency virus (HIV) infection. Mortality in HIV patients is now more commonly caused by non-acquired immunodeficiency syndrome (AIDS)-defining conditions, and life expectancy is approaching that of the non-HIV-infected population. Similarly, over the past decade, mortality of HIV patients in the intensive care unit (ICU) has decreased from nearly 90% to 20%, and reasons for admission have evolved from AIDS to non-AIDS conditions. Therefore, critical care specialists can expect to care for more HIV-infected patients admitted to the ICU for complications related to their HIV infection or their treatment or non-HIV-related disorders. This chapter presents considerations regarding HIV-infected patients that may result in their admission to the ICU or that may complicate their ICU care.

HIV-Related Complications

Although HIV-related complications may occur throughout the entire spectrum of immunodeficiency, certain conditions are unusual until a patient's $CD4^+$ lymphocyte falls to less than a certain threshold (Tables 23.1 and 23.2). Furthermore, as the patient's $CD4^+$ lymphocyte counts continue to decline below these thresholds, the risk for these complications increases.

Pulmonary Complications

BACTERIAL PNEUMONIAS

In the past, pneumonias were the most common cause for hospitalization of HIV-infected patients. Acute onset of cough and fever with a lobar radiographic infiltrate suggests bacterial pneumonia. Not only do HIV-infected patients have rates of pneumonia resulting from *Streptococcus pneumoniae* that are 150-fold greater than those in the non-HIV-infected population, but they also are at higher risk for recurrences. Because immunologic response to the polysaccharide antigens is impaired at $CD4^+$ lymphocyte counts less than 500 cells/μL and in patients with detectable viral loads, pneumococcal vaccination should *not* be considered as protective in HIV-infected individuals. Furthermore, HIV-infected patients with pneumococcal pneumonia have a greater risk for bacteremia, meningitis, and other complications compared to than non-HIV-infected individuals.

Likewise, *Haemophilus influenzae* pneumonia occurs 100 times more often in HIV-infected versus non-HIV-infected patients. Because the organisms for most of these *Haemophilus* species cannot be typed, *H. influenzae* type b vaccine is also not protective. Although other pyogenic bacteria are less common causes of pneumonia in HIV-infected patients, *Pseudomonas aeruginosa*

TABLE 23.1 ■ **Thresholds of CD4+ Lymphocyte Counts and Disease Manifestations for Selected Pathogens**

Pathogen	Common Disease Manifestations	Threshold of CD4+ Lymphocyte Count*
Bacteria		
Streptococcus pneumoniae	Pneumonia, bacteremia, meningitis	500
Haemophilus influenzae	Pneumonia, bacteremia	500
Mycobacterium tuberculosis	Pneumonia	300
Salmonella	Diarrhea, bacteremia	300
Campylobacter, Shigella	Diarrhea	300
Clostridium difficile	Colitis	50
M. avium intracellulare	Cytopenias, fever, abnormal liver function test results, wasting	50
Parasites		
Pneumocystis jirovecii	Pneumonia	200
Giardia	Diarrhea	200
Toxoplasma gondii	Ring-enhancing CNS lesions	100
Cryptosporidium, Isospora	Diarrhea	100

*The CD4+ lymphocyte count (cells/μL) when each complication may be first encountered. The risk for each complication continues to increase as the CD4+ lymphocyte count declines further.
CNS, central nervous system.

TABLE 23.2 ■ **Thresholds of CD4+ Lymphocyte Counts and Disease Manifestations for Selected Noninfectious Complications**

Complication	Common Disease Manifestations	Threshold of CD4+ Lymphocyte Count*
Immune thrombocytopenic purpura	Thrombocytopenia	500
Non-Hodgkin lymphoma	Adenopathy, wasting	300
Nephropathy	Nephrotic syndrome, renal insufficiency	200
Cardiomyopathy	Congestive heart failure	100
CNS lymphoma	Ring-enhancing CNS lesions	50

*The CD4+ lymphocyte count (cells/μL) when each complication may be first encountered. The risk for each complication continues to increase as the CD4+ lymphocyte count declines further.
CNS, central nervous system.

pneumonia may be seen in late stages of disease (usually associated with a CD4+ lymphocyte count < 100 cells/μL, cavitary lung disease, or prior treatment with broad spectrum antibiotics). In addition, *Staphylococcus aureus*, including methicillin-resistant strains, is an increasingly common cause of community-acquired pneumonia in HIV-infected patients and should be suspected in patients with a history of viral respiratory infection, intravenous drug use, or severe bilateral infiltrates (Chapter 65). *Legionella* pneumonia occurs infrequently, but its incidence is increased 40-fold in HIV-infected versus non-HIV-infected patients.

Empiric treatment of HIV patients with community-acquired pneumonia requiring ICU admission includes an intravenous (IV) beta-lactam plus either azithromycin or a respiratory fluoroquinolone (moxifloxacin or levofloxacin 750 mg daily) (Chapters 18 and 65). For patients

with those risk factors for *Pseudomonas* pneumonia listed above, the preferred beta-lactam agents include piperacillin-tazobactam, cefepime, imipenem, and meropenem. Vancomycin or linezolid should be added to the antibiotic regimen if Staphylococcus is suspected.

PNEUMOCYSTIS PNEUMONIA

Acquired immunodeficiency syndrome (AIDS) is the most common predisposing cause of *Pneumocystis (carinii) jirovecii* pneumonia (PCP). In the absence of chemoprophylaxis, more than 80% of patients with AIDS develop PCP in their lifetimes. Its likelihood is affected by the degree of immunologic impairment. In HIV-infected adults, this disease most commonly arises in individuals with $CD4^+$ lymphocyte counts between 50 and 75 cells/μL and is uncommon in individuals with $CD4^+$ lymphocyte counts > 200 cells/μL or a $CD4^+$ lymphocyte percentage > 20% of the absolute lymphocyte count.

Early diagnosis and therapy for PCP are associated with a more favorable outcome. Prognosis is worse if the patient has a large alveolar-arterial (A-a) oxygen difference (PAO_2-PaO_2) at presentation, extensive infiltrates on chest radiographs, neutrophilia in a bronchoalveolar lavage (BAL) specimen, elevated serum lactate dehydrogenase (LDH) levels (> 500 IU/L), worse acute physiologic derangements, or chronic comorbidities.

Spontaneous pneumothorax is the most common complication and may occur in up to 10% of patients with PCP. The resulting bronchopleural fistulas may need chemical pleurodesis for closure.

Diagnostic Considerations

PCP is rare in HIV-infected patients with $CD4^+$ lymphocyte counts > 200 cells/μL or > 20% of the absolute lymphocyte count. Elevated lactate dehydrogenase levels are present in more than 90% of hospitalized patients with PCP.

The classic PCP chest radiograph exhibits diffuse, bilateral interstitial infiltrates that extend from the perihilar region and spare the apices. More extensive disease can have an alveolar pattern. In up to 30% to 40% of cases, however, chest radiographs are normal. Moreover, in 10% to 30% of patients, atypical patterns can be seen, especially in those receiving inhaled pentamidine as PCP prophylaxis. These patterns include unilateral or asymmetric disease, single or multiple nodules, cysts or cavities, pneumatoceles, pneumothorax, hilar adenopathy, and pleural effusions.

Because it is unusual for PCP to occur in patients who are taking prophylactic trimethoprim-sulfamethoxazole (TMP-SMX) (co-trimoxazole) appropriately, alternative diagnoses should be sought in such patients with an illness resembling PCP. If PCP does occur in individuals receiving TMP-SMX prophylaxis, it presents atypically. For example, patients may have a protracted time course, with fever rather than cough as the predominant symptom. Conversely, in any HIV-infected patient not receiving TMP-SMX prophylaxis, PCP should be considered in the differential diagnosis of fever of unknown origin, even if the chest radiograph is normal and there is no hypoxemia. Establishing a definitive diagnosis should be attempted in all patients suspected of having PCP. This requires visualization of the organism in pulmonary secretions or a lung biopsy specimen. As many as 20% of HIV-infected individuals who present with clinical, laboratory, and radiographic evidence consistent with PCP have other diagnoses. In addition, patients who are treated empirically for PCP have a worse outcome than those in whom a definitive diagnosis is made. Therefore, empirical treatment for PCP is generally *not* recommended.

Induced sputum after ultrasonic nebulization of hypertonic saline may diagnose PCP in 15% to 90% of cases, depending on local experience and expertise. It is, however, rarely diagnosed in expectorated sputum without induction. When induced sputum testing is not available or yields a negative result, fiberoptic bronchoscopy should be performed. Specimens obtained by bronchoalveolar lavage (BAL) have a diagnostic yield of 86% to 97%, especially if BAL of both lungs is performed.

BAL is more sensitive than standard bronchial washing and brushing. Transbronchial lung biopsy (TBBx) has a sensitivity similar to BAL but may detect some cases missed by BAL. When TBBx is combined with BAL, some centers report a sensitivity of 100%. Evidence suggests that BAL is not sufficient as a single modality to diagnose PCP in patients receiving aerosolized pentamidine for prophylaxis. In this setting, it should always be combined with TBBx.

Plasma (1, 3)-beta-D-glucan, a component of the cell wall of many fungi, including *P. jirovecii,* is often elevated in patients with PCP. The sensitivity of levels > 80 pg/mL are 92% with a specificity of 65%. The test is likely more sensitive than induced sputum at many centers, and it may reduce the need for bronchoscopy or aid in the diagnosis for patients who are not candidates for bronchoscopy.

Treatment

Treatment for PCP that is severe enough to need admission to the ICU should be initiated with TMP-SMX administered intravenously at a dose of 15 to 20 mg trimethoprim/kg/day divided into three or four doses. Patients who are intolerant to sulfonamides should be treated with pentamidine isethionate (a single IV dose of 3 to 4 mg/kg/day). Survival is better in patients with severe disease ($P(A\text{-}a)O_2 > 45$ mm Hg or $Pao_2 < 70$ mm Hg on ambient air) if they are also treated with corticosteroids (prednisone 40 mg twice a day or methylprednisolone IV 30 mg twice daily for 5 days followed by a taper over 15 days). Although the benefit of corticosteroids initiated 72 hours after the start of antimicrobial therapy is uncertain, they still are recommended.

Some patients may experience a fall in oxygenation and a progression of infiltrates on the chest radiograph during the first 7 days of treatment. Therefore, if no improvement is evident by the end of the first week of therapy, patients who have not had a definitive diagnosis of PCP established should undergo bronchoscopy expeditiously. For patients in whom the diagnosis of PCP has been established, a second pulmonary pathogen should be sought.

MYCOBACTERIAL INFECTIONS

HIV infection is the most significant predisposing factor for reactivation of latent *Mycobacterium tuberculosis* (TB) infection. Up to 50% of HIV-infected patients who are infected with TB eventually develop active TB. Although it occurs most commonly when a patient's $CD4^+$ lymphocyte count is < 350 cells/μL, it can occur at higher $CD4^+$ counts, with a presentation similar to TB in non-HIV-infected patients, including subacute or chronic onset of fever, weight loss, cough, chest pain, and shortness of breath.

Patients with low $CD4^+$ lymphocyte counts also have a high risk of extrapulmonary TB (40% to 80% of TB cases). Disseminated TB and lymphadenitis are the two most common presentations of extrapulmonary disease. Disseminated disease may present acutely with hypotension and respiratory distress. TB lymphadenitis is most commonly located in cervical, supraclavicular, or axillary nodes, but intrathoracic and intra-abdominal nodes can be seen. Central nervous system (CNS) infection occurs in 5% to 10% of HIV-infected patients with TB.

Chest radiographs of active TB infection vary by level of immunosuppression. Patients with high $CD4^+$ counts often have apical cavity disease. Those with low counts infrequently have cavitation but more often have lower lobe consolidation, intrathoracic adenopathy, miliary infiltrates, and pleural effusions.

Reactivity to tuberculin skin testing is inversely related to $CD4^+$ counts. Among patients with AIDS and active TB, only 10% to 30% of patients will have a skin test reaction that is greater than or equal to 10 mm of induration. Sputum is positive by microscopy for acid-fast bacilli (AFB) in 40% to 65% of HIV-infected patients with active TB, and it is positive by AFB culture in 75% to 95% of patients. For patients who have not had a diagnosis made from sputum, BAL is diagnostic by AFB smear in 7% to 20% of patients and by culture in 52% to 89% of individuals, whereas

transbronchial biopsy specimens result in positive AFB smears in 10% to 39% of patients and in positive cultures in 42% to 85% of individuals.

TB should be considered in the differential diagnosis of any suspected infection in an HIV patient born in the developing world. Patients with diagnosed or suspected TB should be started on four-drug therapy as soon as possible, with isoniazid, rifampin, ethambutol, and pyrazinamide, pending drug susceptibility testing. Resistance to first-line TB agents should be suspected in patients with a history of previous TB treatment, poor adherence, homelessness, sputum smear positivity after 2 months of TB therapy or culture positivity after 3 months of therapy, and birth or residence in an area of the world where multidrug resistant (MDR)-TB is endemic. In such cases, consideration should be given for the addition of two additional agents, typically a fluoroquinolone and amikacin. Adjunctive steroids should be administered for CNS or pericardial infection, beginning with IV dexamethasone 0.3 to 0.4 mg/kg followed by a switch to oral therapy with clinical improvement and a slow taper. There are numerous drug-drug interactions between the rifamycins and antiretroviral drugs in multiple therapeutic classes. Modification of antiretroviral therapy may be required in patients started on rifampin. Despite these drug-drug interactions, a rifamycin should always be used to treat TB in patients with HIV infection owing to improved outcomes.

Among the nontuberculous mycobacteria, *Mycobacterium avium* complex (MAC) and *Mycobacterium kansasii* are the most common causes of pulmonary infection. Although isolated pulmonary disease can occur, MAC more commonly presents with disseminated disease as well as signs and symptoms of chronic disease (prolonged fever, weight loss, diarrhea, cytopenias, and low albumin levels). When MAC presents as pulmonary disease, the chest radiograph typically shows bilateral, interstitial-nodular infiltrates, indistinguishable from PCP. MAC may be a copathogen or colonizer in HIV-infected patients with other causes of pneumonia. Under these circumstances, the organism is often cultured from a BAL specimen as a single or rare colony and requires no treatment. *M. kansasii* infection presents primarily as pulmonary disease.

Neurologic Complications

During the course of untreated disease, the majority of HIV-infected patients experience one or more neurologic complications. Some of these—for example, meningoencephalitis, seizures, and focal neurologic deficits—may lead to admission to the ICU.

CRYPTOCOCCAL MENINGITIS

Cryptococcal meningitis, the most common manifestation of cryptococcal infection in HIV-infected patients, typically presents with headache, fever, nausea, vomiting, and no focal neurologic findings. About 10% of patients present with seizures. Cryptococcal disease starts as a pulmonary infection and then disseminates to the brain and other organs. Cutaneous disease is present in 10% of patients, typically appearing as multiple nonpigmented nodular lesions that are often mistaken for molluscum contagiosum.

The diagnosis is made by cerebrospinal fluid (CSF) analysis. The CSF white blood cell count is typically elevated, with a predominance of lymphocytes, but it may be normal in 20% of cases. CSF protein levels are also typically elevated, whereas CSF glucose levels are normal or decreased. The CSF cryptococcal antigen is positive in nearly all HIV-infected patients with cryptococcal meningitis and has a sensitivity comparable to a CSF fungal culture. Because of a high fungal burden, the India ink test produces positive results in 60% to 80% of cases. *Serum* cryptococcal antigen is positive in 95% of cases and can be diagnostic in the appropriate clinical setting when a lumbar puncture cannot be obtained. Imaging studies of the brain, however, are usually normal. Evaluation for CNS disease should be performed in all patients with *Cryptococcus* diagnosed in lung or in blood.

Amphotericin B (0.7 to 1.0 mg/kg/day) is the initial therapy. For patients with renal dysfunction, lipid formulations of amphotericin B at a dose of 4 to 6 mg/kg daily should be considered. The addition of 5-flucytosine (100 mg/kg/day in four divided doses) to amphotericin B sterilizes the spinal fluid more rapidly but does not improve clinical outcome. Because patients given initial therapy with fluconazole, 400 mg/day, have a higher mortality rate during the first 7 days of therapy, it should be reserved for chronic maintenance therapy after the completion of a 2-week induction course of amphotericin B. Mortality is increased in patients who present with mental status abnormalities, cranial nerve palsies, ataxia, or elevated intracranial pressure (ICP). Treatment directed at reducing ICP, such as daily lumbar punctures, acetazolamide, and ventriculoperitoneal shunting, should be performed for asymptomatic patients with ICP > 32.0 cm H_2O (23.5 mm Hg) and for symptomatic patients with ICP > 18.0 cm H_2O (13.2 mm Hg).

BACTERIAL MENINGITIS

Acute bacterial meningitis is less common than cryptococcal meningitis in HIV-infected individuals. The most common causes are *S. pneumoniae* and *H. influenzae*. Less common causes are *Listeria monocytogenes*, *M. tuberculosis*, endemic fungi (histoplasmosis and coccidioidomycosis), and neurosyphilis.

TOXOPLASMA ENCEPHALITIS

The most common *focal* neurologic complication of HIV infection is *Toxoplasma* encephalitis. The risk of *Toxoplasma* encephalitis developing in HIV-infected patients with $CD4^+$ lymphocyte counts less than 100 cells/μL is 20% to 30% per year in the absence of prophylaxis. It almost always results from reactivation of latent infection and presents as a subacute headache with focal neurologic findings in the majority of patients and as seizures in about 30% of patients. The diagnosis is made empirically after the detection of multiple ring-enhancing lesions on brain imaging in a patient with a positive serum toxoplasma serologic profile. A magnetic resonance imaging (MRI) study of the brain with gadolinium enhancement is the most sensitive imaging test and is preferred over a computed tomographic (CT) scan with contrast. Serologic studies are falsely negative in 10% of cases. Spinal fluid analysis is often normal and unhelpful in making the diagnosis.

The preferred treatment is pyrimethamine (100- to 200-mg loading dose and then 50 to 100 mg/day) plus folinic acid (10 mg/day) and sulfadiazine (4 to 8 g/day). For patients who are allergic to sulfonamide, clindamycin (900 to 1200 mg intravenously or 300 to 450 mg orally), azithromycin (1200 mg/day) or clarithromycin (1 g twice per day) may be substituted for the sulfadiazine. After 2 or 3 weeks of treatment, patients should undergo repeat brain imaging. Failure to observe shrinkage of the ring-enhancing lesions suggests another diagnosis, and a brain biopsy may be indicated. Approximately 10% of patients with *Toxoplasma* encephalitis fail to demonstrate a response on imaging studies within the first 3 weeks of therapy. Assuming that a radiologic response to treatment has been observed, chronic lifelong suppressive therapy with reduced doses of drug is started after a 6-week course of induction therapy.

OTHER CAUSES OF FOCAL NEUROLOGIC DISEASE

Primary central nervous system lymphoma is the second most common cause of *focal* CNS complications in HIV-infected patients. Like CNS toxoplasmosis, the presenting symptoms of CNS lymphoma depend on the neuroanatomic location of the lesions. CNS lymphoma cannot be distinguished from CNS toxoplasmosis on clinical or radiologic grounds. However, the presence of Epstein-Barr virus by polymerase chain reaction (PCR) in CSF is suggestive of CNS lymphoma.

The therapeutic algorithm for a patient with ring-enhancing CNS lesions begins with empirical therapy for toxoplasmosis (even in the absence of a positive serologic test result). Patients in whom a 2- to 3-week trial of anti-*Toxoplasma* therapy does not decrease the size of the ring-enhancing lesions are likely to have CNS lymphoma. However, a brain biopsy is required for a definitive diagnosis. Although primary CNS lymphoma may respond to radiation therapy, survival after diagnosis is only ~3 months.

Progressive multifocal leukoencephalopathy (PML), a disease of white matter caused by JC virus (not related to the Jakob-Creutzfeldt syndrome), is the third most common cause of focal CNS pathology in HIV-infected patients. PML occurs in less than 5% of HIV-infected patients. Its clinical presentation also depends on the location of the lesions. Common manifestations include seizures, and focal motor and sensory defects, including aphasia, visual field defects, and ataxia (when disease is present in the cerebellum). MRI reveals single or multiple white matter lesions without surrounding edema or mass effect. JC virus DNA by PCR can be detected in CSF in 70% to 90% of cases of PML and is diagnostic. Although there is no proven therapy for PML, improvement in immunologic function after the initiation or modification of antiretroviral therapy has resulted in clinical and radiographic improvement in some patients.

Differential Diagnosis of Hypotension in the Patient with Human Immunodeficiency Virus Infection

BACTERIAL CAUSES

Bacterial sepsis is an important and underappreciated cause of death in HIV-infected patients. HIV-infected patients often have neutropenia secondary to the bone marrow dysfunction of HIV infection, infectious complications or malignancies, or toxicities of several commonly used medications. Although HIV-infected patients are at an increased risk of bacteremia when absolute neutrophil counts fall to < 1000 cells/μL, their risk appears to be less than that of oncology patients with chemotherapy-induced neutropenia of the same level.

Pneumococcal bacteremia complicating pneumonia is the most common cause of bacteremia in HIV-infected patients. HIV-infected patients are also at increased risk for staphylococcal bacteremia. This is probably the result of cutaneous complications of HIV disease providing a route for systemic entry. Staphylococcal infection also may present as pyomyositis, typically of the large muscle groups of the thigh, and should be considered the probable diagnosis in an HIV-infected patient presenting with fever and a painful or swollen leg.

Infection with *Salmonella* species (non–*S. typhi*) is another common cause of bacteremia in HIV-infected patients and can be seen in the absence of diarrhea or other symptoms related to the gastrointestinal tract.

Pseudomonas bacteremia should be considered in HIV-infected patients receiving chronic antibiotic therapy for the prophylaxis of opportunistic infections or the treatment of complications such as sinusitis. Finally, histoplasmosis and TB can present with fever and hypotension in patients with endemic exposure.

VOLUME-DEPLETION CAUSES

Diarrhea in the HIV-infected patient may lead to intravascular volume depletion and hypotension. This may be caused by enteric bacterial pathogens (*Salmonella, Shigella,* and *Campylobacter*), parasites *(Giardia, Isospora belli, Cryptosporidium*, *Microsporidia),* and viruses (most commonly cytomegalovirus). HIV-infected patients may have diarrhea caused by *Clostridia difficile* colitis, even without a history of current or recent antibiotic use.

Although HIV patients with MAC typically present with chronic fevers and weight loss, they can appear acutely ill if they become volume depleted because of concomitant diarrhea.

ADRENAL INSUFFICIENCY

Adrenal insufficiency should also be considered in any HIV-infected patient with a low $CD4^+$ lymphocyte count presenting with hypotension and no other cause. The major risks for adrenal insufficiency in HIV-infected patients include infection with cytomegalovirus, TB, or MAC.

Other Organ System Dysfunction in Patients Infected with Human Immunodeficiency Virus

CARDIAC DISORDERS

Common cardiac complications of HIV infection include valvular heart disease, pericarditis, and myocarditis. Valvular disease can be caused by infectious endocarditis, especially in IV drug users, or by marantic endocarditis complicating malignancies, such as Kaposi sarcoma and lymphoma.

Pericarditis can be infectious (TB or MAC), noninfectious (lymphoma), or idiopathic. Idiopathic pericarditis often presents as tamponade and requires pericardiocentesis. However, it usually does not reaccumulate after drainage.

A late manifestation of HIV infection is dilated cardiomyopathy, characterized pathologically by focal myocarditis with round cell infiltration and myocardial fiber necrosis. Patients typically present in congestive heart failure. Its cause is not well understood, but in a small percentage of cases, it may be a complication of nucleoside reverse transcriptase inhibitors. In other cases, it has improved after antiretroviral therapy was initiated.

HEMATOLOGIC DISORDERS

Cytopenias are seen in most HIV-infected individuals. Anemia is usually normochromic, normocytic, and multifactorial, but impaired erythropoiesis is almost always a contributing factor. Although the proportion of HIV-infected patients who have positive Coombs test results increases with more advanced disease, immune hemolysis is unusual.

Granulocytopenia also increases with progressive disease. Myelotoxicity can be caused by zidovudine, sulfonamides, or ganciclovir. Filgrastim (granulocyte colony-stimulating factor [GCSF]) is indicated in patients with neutrophil counts < 500 cells/μL.

Thrombocytopenia can be encountered at all stages of disease, independent of other cytopenias. Megakaryocytes can be infected with HIV, leading to decreased production of platelets. Immune thrombocytopenic purpura accounts for thrombocytopenia in many patients, but despite platelet counts falling to < 10,000/μL, bleeding is rare. Effective antiretroviral therapy may improve platelet counts. Prednisone (30 to 60 mg/day) and IV immunoglobulin (400 mg/day for 2 to 5 days) can increase platelet counts. This lasts for 2 to 4 weeks in the majority of patients with thrombocytopenia resulting from immune destruction. Splenectomy produces a durable increase in platelet counts in about half the patients undergoing this procedure (see also Chapter 63).

RENAL DISORDERS

HIV-associated nephropathy (HIVAN), which is most common in African American patients with low $CD4^+$ lymphocyte counts, can also occur earlier in the course of disease. Patients typically present with nephrotic syndrome or renal insufficiency. Ultrasonography often reveals large kidneys with increased echogenicity, a feature that can distinguish HIVAN from other causes of

chronic renal disease in which kidney size is often small. The development of renal insufficiency is frequently rapid, especially in patients with nephrotic syndrome. The median time from presentation to dialysis is only 11 weeks. Renal function may improve after the initiation of antiretroviral therapy with or without short courses of high-dose prednisone.

Renal insufficiency can also be caused by several drugs that are frequently used in HIV-infected patients. Tenofovir, pentamidine, foscarnet, TMP-SMX, amphotericin B, sulfadiazine, and rifampin can cause acute tubular necrosis or acute tubulointerstitial nephritis. Cobicistat inhibits tubular secretion of creatinine and causes a predictable creatinine increase of 0.15 to 0.20 mg/dL after its initiation; higher increases should prompt an evaluation for other causes of renal dysfunction.

ELECTROLYTE DISORDERS

Hyponatremia is the most frequent electrolyte disturbance in hospitalized HIV-infected patients and is due to inappropriate secretion of antidiuretic hormone, hypovolemia, or adrenal insufficiency. *Hypernatremia* can be seen secondary to drug-induced nephrogenic diabetes insipidus caused by foscarnet or amphotericin B.

Hypokalemia occurs as a result of gastrointestinal losses from diarrhea, or vomiting, or urinary losses caused by drug-induced tubular acidosis (e.g., from amphotericin B). *Hyperkalemia* has been reported in association with high-dose trimethoprim administration used to treat patients with PCP and renal insufficiency.

Lactic acidosis, secondary to nucleoside reverse transcriptase inhibitor therapy, has been documented in the absence of tissue hypoxia in patients with HIV infection. Zidovudine, didanosine, and stavudine are the agents most commonly implicated, but any drug in the class may be the cause. These patients present with gastrointestinal symptoms, subacute malaise, fatigue, and hyperventilation and have an anion gap acidosis with high plasma lactate levels. Death from progressive acidosis rapidly ensues in the majority of patients.

DRUG TOXICITIES AND DRUG-DRUG INTERACTIONS

Many drugs used to treat HIV infection and its complications may directly cause potentially life-threatening toxicities. They also can cause toxicity from drug-drug interactions. Drug toxicity should be considered in the differential diagnosis of any condition not attributed to an HIV-related opportunistic infection or malignancy. This is especially true for patients receiving ritonavir, a potent inhibitor of several isoforms of cytochrome P_{450}, or cobicistat, a more selective inhibitor with no antiviral activity that is used only to boost the concentration of companion antiretroviral agents. As a consequence, a number of drugs are contraindicated in patients receiving these agents. One should do a careful review for potential drug-drug interactions prior to placing orders for any new drug (see www.hiv-druginteractions.org, accessed August 9, 2012, and Tseng and Foisy, 2012, in the online bibliography).

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

HIV patients initiating or resuming antiretroviral therapy with low CD4+ T cell counts may experience a potent pathogen-specific immune response that leads to the development of new or worsening symptoms that have been termed the immune reconstitution inflammatory syndrome (IRIS). IRIS is manifest in two forms: (1) unmasking IRIS refers to a previously undiagnosed disease becoming clinically apparent, and (2) paradoxical IRIS refers to worsening of a previously diagnosed disease. IRIS should be suspected whenever an HIV patient presents with new or worsening symptoms of an opportunistic infection or malignancy within several weeks to 1 year

following the initiation of antiretroviral therapy. IRIS can complicate any opportunistic infection, malignancy, and disease, though critically ill HIV patients are most likely to have conditions involving either the lung or central nervous system.

Pulmonary conditions most commonly associated with IRIS are tuberculosis (TB), pneumocystis pneumonia, cryptococcus, Kaposi sarcoma, nontuberculous mycobacteria, and sarcoidosis, and they generally occur within weeks following the initiation of antiretroviral therapy. Manifestations of IRIS may include new or worsening fevers, worsening respiratory status, new adenopathy, worsening of parenchymal infiltrates, and increased pleural effusions. If the underlying condition has not been previously diagnosed, therapy should be directed at its treatment. If the condition has been previously diagnosed, prednisone at a dose of 1 mg/kg in single or divided doses, or a parenteral steroid at a comparable dose, should be added. Antiretroviral therapy should be continued.

The most common conditions associated with IRIS in the CNS are cryptococcal meningitis, PML, and TB. Paradoxical IRIS complicating cryptococcal meningitis can occur late after initiation of antiretroviral therapy and treatment of the cryptococcal infection. Patients usually present with persistent headache and may exhibit mental status changes. IRIS can be distinguished from recurrent meningitis by the absence of a positive CSF fungal culture. Patients may also need serial lumbar punctures to reduce intracranial pressure associated with communicating hydrocephalus (Chapter 41). New onset or worsening symptoms of PML in the setting of IRIS can exhibit unusual features, including mass effect, and edema and contrast enhancement of CNS lesions on MRI. TB IRIS of the CNS can present as meningitis or new or enlarging tuberculomas. Steroids are indicated for the treatment of IRIS of the CNS, and antiretroviral therapy should be continued.

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CHAPTER 24

Care of the Cancer Patient with Neutropenia or Thrombocytopenia

Daniel J. Landsburg ■ Alison W. Loren

Cancer patients may become critically ill as a result of disease- or therapy-related complications. This is particularly true of patients with hematologic malignancies or those undergoing hematopoietic cell (i.e., bone marrow) transplantation (HCT). One common problem among oncology patients is the development of cytopenias, which, among other issues, can result in life-threatening infection or bleeding. This chapter focuses on the management of neutropenia and thrombocytopenia in the cancer patient requiring admission to the intensive care unit (ICU).

Clinical Disorders

NEUTROPENIA

The absolute neutrophil count (ANC) is defined as follows:

$$\begin{aligned}\text{ANC (cells/}\mu\text{L)} = {} & \text{White Blood Cells (WBCs) (cells/}\mu\text{L)} \\ & \times [\,\%\,\text{mature neutrophils} + \%\,\text{bands}]\end{aligned} \qquad \text{(Equation 24.1)}$$

Mild neutropenia is defined as an ANC of 1000 to 1500 cells/μL, although patients are not commonly referred to as neutropenic until their ANC declines to < 1000 cells/μL. *Moderate* neutropenia is defined as an ANC of 500 to 1000 cells/μL, and *severe* neutropenia as an ANC < 500 cells/μL. In cancer patients, neutropenia can develop as a manifestation of cancer itself (particularly in patients with hematologic malignancies) or as an expected consequence of cytotoxic chemotherapy. In either case, neutropenic patients are prone to developing infections (which can also be a cause of or further exacerbate neutropenia) and frequently demonstrate inadequate activation of their immune and inflammatory systems when challenged with an infection. Accordingly, the development of fever in a neutropenic patient is considered a medical emergency that requires immediate action (refer to "Febrile Neutropenia" later in this chapter).

Identifying the etiology of neutropenia can be useful in predicting its expected duration and depth. The duration of chemotherapy-induced neutropenia varies based on the particular drug regimen but is almost always brief and largely predictable. In general, the white blood cell (WBC) count will begin to decline within 5 to 7 days from the initiation of chemotherapy, which is followed by a period of moderate to severe neutropenia of 3 to 10 days in duration. The lowest point (i.e., lowest WBC count) is referred to as the *nadir*. In most instances, the bone marrow is expected to recover fully and neutropenia will resolve accordingly. However, timing of the nadir and recovery may vary in patients with underlying bone marrow dysfunction resulting from the malignancy itself, effects of repeated cycles of cytotoxic chemotherapy, or marrow suppression sometimes associated with infection, and also depends on the chemotherapeutic agents administered.

BOX 24.1 ■ Differential Diagnosis of Neutropenia in the ICU Cancer Patient

- Malignancy
  - Bone marrow involvement with myeloid or lymphoid malignancy
  - Bone marrow failure due to aplastic anemia or other syndromes
  - Bone marrow invasion by carcinoma
- Drug toxicity
  - Cytotoxic chemotherapy
  - Non-chemotherapy medication
- Infection (with or without sepsis)
- Inadequate engraftment after hematopoietic cell transplantation
- Autoimmune granulocyte destruction

Neutropenia can also occur prior to the initiation of chemotherapy in patients with hematologic malignancies, particularly acute myelogenous leukemia (AML) and the closely related myelodysplastic syndromes (MDS), as well as acute lymphoblastic leukemia (ALL). Neutropenia is infrequently seen in patients with chronic lymphocytic leukemia (CLL) and may be attributed to bone marrow replacement with CLL or, in rare cases, to autoimmunity. Additionally, the nonmalignant condition of severe aplastic anemia is manifested by neutropenia as well as other cytopenias. The degree and duration of neutropenia associated with these diseases can vary greatly, and the actual duration may be unknown in a patient who is newly diagnosed. Unfortunately, patients with hematologic malignancies frequently remain neutropenic until their underlying disease responds to therapy, which can take weeks or even months in some cases.

Finally, neutropenia almost always develops during allogeneic (donor) and autologous (self) hematopoietic cell transplantation as a result of *conditioning* with high doses of chemotherapy, radiation therapy, or both. Cancer patients receiving these therapies typically remain neutropenic until the time of *engraftment* (i.e., the production of new blood cells). This period of neutropenia typically lasts for 2 to 3 weeks, although it is not uncommon for the duration to be shorter in patients receiving reduced-intensity or nonmyeloablative conditioning regimens for allogeneic transplants. Nevertheless, these patients are highly immunocompromised because of the presence of a donor-derived immune system as well as the need for immunosuppressive medical therapy such as calcineurin inhibitors. The details of hematopoietic cell transplantation are beyond the scope of this chapter. However, the ICU provider should always seek consultation from the hematology-oncology service when managing patients undergoing this treatment modality because of the profound immunosuppression and other unique features associated with this form of therapy.

Box 24.1 gives the differential diagnosis for neutropenia in the ICU cancer patient.

THROMBOCYTOPENIA

Thrombocytopenia is defined as a platelet count of < 150,000 cells/μL, although clinically significant bleeding rarely occurs at a platelet count of > 50,000 cells/μL unless disseminated intravascular coagulation (DIC) coexists. The risk of spontaneous bleeding is highest when the platelet count is < 10,000 cells/μL. The etiology of thrombocytopenia in cancer patients is often related to the disease or its therapy (Box 24.2), but causes may also be similar to those seen in the general population (which are addressed in more detail in Chapters 45 and 63).

As with neutropenia, thrombocytopenia in cancer patients can be associated with chemotherapeutic agents in both standard and high doses as well as hematologic malignancy. Infection with or without evidence of sepsis is common in oncology patients and can be associated with thrombocytopenia as well. Isolated thrombocytopenia in the oncology patient may be the result of etiologies seen in the general population such as (nonchemotherapy) drug-induced thrombocytopenia

BOX 24.2 ■ Differential Diagnosis of Thrombocytopenia in the ICU Cancer Patient

Malignancy
- Bone marrow involvement with myeloid or lymphoid malignancy
- Bone marrow failure due to aplastic anemia or other syndromes
- Bone marrow invasion by carcinoma

Drug toxicity
- Cytotoxic chemotherapy
- Non-chemotherapy medication (particularly heparin)*

Infection (with or without sepsis)
Inadequate engraftment after hematopoietic cell transplantation
Disseminated intravascular coagulation (DIC)*
Idiopathic thrombocytopenic purpura (ITP)*
Thrombotic thrombocytopenic purpura (TTP)*
Splenic sequestration of platelets*
Autoimmune destruction of platelets*

**See Chapters 45 and 63 for more details regarding these diagnoses.*

including heparin-induced thrombocytopenia (HIT) as well as DIC, thrombotic thrombocytopenic purpura (TTP), or idiopathic thrombocytopenic purpura (ITP) (see Chapters 45 and 63).

In particular, thrombocytopenia associated with a coagulopathy (whether apparent clinically or by laboratory testing) with or without microangiopathic hemolytic anemia (MAHA) should raise suspicion for DIC, which is manifested by consumption of elements in the coagulation cascade resulting in hemorrhage or thromboses. Acute DIC is a well-recognized complication of acute promyelocytic leukemia (APL) as well as sepsis, whereas chronic DIC is more commonly associated with solid tumor malignancies.

Finally, another cause of thrombocytopenia associated with MAHA but not usually a prolonged PT/PTT is thrombotic thrombocytopenic purpura (TTP), an abnormality of hemostasis characterized by the formation of platelet thrombi often leading to end-organ damage. Analogous to this diagnosis is that of transplantation-associated thrombotic microangiopathy, which is a phenomenon seen in the setting of allogeneic hematopoietic cell transplantation and may be attributed to conditioning chemotherapy or radiation therapy or to the calcineurin inhibitors used for posttransplantation immunosuppression.

Box 24.2 gives the differential diagnosis for thrombocytopenia in the ICU cancer patient.

Diagnostic Evaluation

A thorough history and physical examination are the first steps in properly evaluating a cancer patient with neutropenia or thrombocytopenia admitted to the ICU. If possible, patients or families should be questioned regarding any recent or current signs or symptoms of infections of the upper and lower respiratory system, gastrointestinal system including the rectum, urinary tract, and skin (particularly in those with indwelling vascular or urinary catheters). Patients with thrombocytopenia should be asked about signs or symptoms indicative of major bleeding events such as intracranial, pulmonary, and gastrointestinal hemorrhage as well as more minor events including epistaxis, gingival bleeding, hematuria, or the development of ecchymoses or petechiae.

Certain physical exam maneuvers are crucial to the evaluation of neutropenic and thrombocytopenic cancer patients. The skin should be carefully inspected for any areas of infection, particularly at or around sites of indwelling catheters (discussed later), as well as for petechiae and

ecchymoses. Visualization of the oropharynx can reveal thrush, dental infections, gingival bleeding or mucositis, which is common in patients receiving chemotherapy. The abdomen should be examined for evidence of tenderness, which could indicate abscess or hemoperitoneum, as well as splenomegaly, which may contribute to thrombocytopenia. A digital rectal exam should *not* be performed on neutropenic patients because there is a high risk of provoking bacterial translocation into the bloodstream with manipulation of the rectum, but a visual examination is appropriate. It is important to note that neutropenic patients often lack the ability to produce a normal inflammatory response and may not demonstrate typical signs of infection.

Relevant laboratory testing in these patients includes a complete blood count (CBC) with differential along with a review of a peripheral blood smear. These tests will confirm neutropenia (which can occur even when a leukocytosis is present) and allow for evaluation for immature white blood cell forms or blasts indicative of acute leukemia and for the presence of toxic granulations or Döhle bodies in peripheral neutrophils (indicating severe acute inflammation). Additional blood testing should include serum chemistry panel, liver function tests, uric acid level, and lactic dehydrogenase (LDH) to evaluate for metabolic abnormalities resulting from rapid cell destruction termed *tumor lysis syndrome*, and finally prothrombin/partial thromboplastin times (PT/PTT), fibrinogen, fibrin split products, and D-dimer to assess for the presence of DIC. Additionally, cultures of the blood (two sets with at least one drawn directly from peripheral blood [Chapter 14]) and urine should be collected in febrile patients (particularly at the onset of a neutropenic fever as discussed later). Radiographic evaluation should be tailored appropriately based on the history and physical exam but almost always includes a chest radiograph. Computerized tomography (CT) scans can be useful in identifying complications of thrombocytopenia and neutropenia such as intracranial hemorrhage, fungal sinusitis, pneumonia, or neutropenic enterocolitis (also termed *typhlitis*) (Chapter 60). Additional diagnostic testing unique to these patients may include a bone marrow aspiration and biopsy, which the hematology-oncology consulting service should perform.

Clinical Management

Listed next are general guidelines for the management of neutropenia and thrombocytopenia in the critically ill cancer patient, with particular focus on the treatment of febrile neutropenia and transfusion-dependent thrombocytopenia.

FEBRILE NEUTROPENIA

Febrile neutropenia, an oncologic emergency, is formally defined as a temperature of ≥ 38.0° C (100.4° F) lasting for ≥ 1 hour or an isolated temperature of ≥ 38.3° C (101.0° F) in a patient with an ANC of < 500 cells/μL. However, clinical practice varies in regard to the practical management of these patients. For example, a neutropenic fever at the authors' hospital is classified by an isolated temperature of ≥ 38.0° C in a patient with an ANC of < 1000 cells/μL. The ICU provider should be mindful of the specific parameters of neutropenic fever designated within his or her hospital and how to respond.

Although infection is not always the underlying cause of fever in the neutropenic patient, this must be assessed for immediately as infection in these patients can be rapidly fatal. At the first instance of febrile neutropenia, a diagnostic workup for infection should be performed. This includes obtaining blood and urine cultures as well as a chest radiograph. Emergent initiation of empiric broad-spectrum antibiotics, with adequate gram-negative/pseudomonal coverage (preferably after cultures are drawn provided there are no delays) is *mandatory* (Figure 24.1).

Cancer patients frequently have indwelling central venous catheters, and, if present, consideration should be given to removing the device. This is particularly relevant in the setting of documented bacteremia or fungemia. Even if the catheter is not deemed to be the likely source of infection, it can

serve as a nidus for circulating pathogens and contribute to a persistent bloodstream infection. If the catheter is removed, the tip should be collected in a sterile fashion and cultured (see Chapter 14). Of course, the decision to remove a central venous catheter should be made with great caution, as it may be the only source of dependable intravenous (IV) access for the delivery of fluids, antibiotics, blood products, and other essential therapies. As mentioned previously, a careful examination of the catheter itself and the surrounding skin can be helpful in identifying potential infection. Tenderness to palpation of the skin along the path of a tunneled central venous catheter is a finding that is particularly concerning for infection, and it should prompt urgent consultation with either the interventional radiology or the surgical team to evaluate for extraction.

A suggested approach to the management and treatment of febrile neutropenia in the ICU is presented in Figure 24.1. The cornerstone of treatment is the empiric initiation of an antibiotic

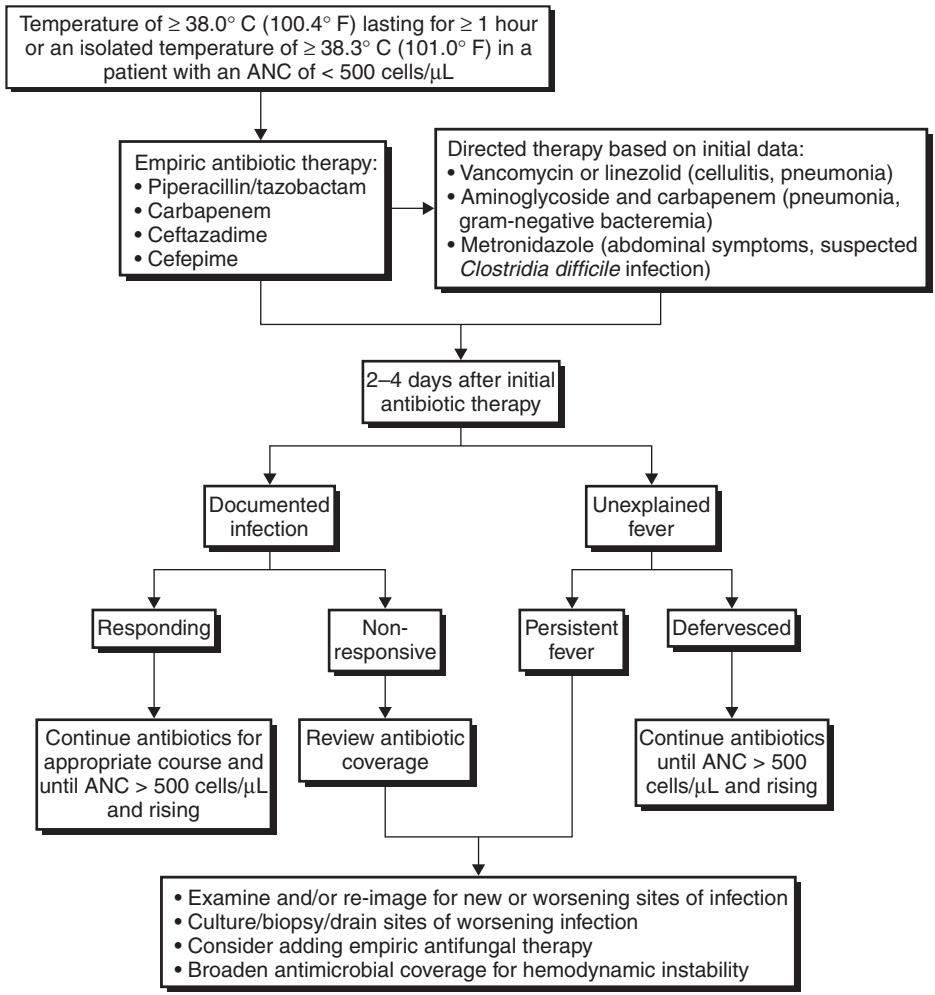


Figure 24.1 Schematic flow diagram of treatment of patients with febrile neutropenia in the intensive care unit. *(Adapted from Freifeld A, Bow EJ, Sepkowitz KA, et al: Clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 52(4):e56-e93, 2011.)*

with activity against *Pseudomonas* within 1 hour of the documentation of fever. Gram-negative infections are common among neutropenic patients and can be rapidly fatal (even if managed appropriately). "Double-coverage" using a second agent with activity against gram-negative bacteria is not required but should be strongly considered in a patient with severe sepsis or septic shock (Chapter 10). Adding additional empiric coverage against gram-positive bacteria is not required with the first neutropenic fever unless there is specific clinical concern for an infection likely to be caused by these organisms such as that of the skin or soft-tissue or an indwelling catheter or, again, if signs of severe sepsis or septic shock are present.

Even if the patient is persistently febrile, antibiotics are not generally changed for the first 48 hours following the initial neutropenic fever, unless an additional source of untreated infection becomes apparent. Even if diagnostic testing reveals a clear source of infection, broad-spectrum antibiotic therapy should continue without narrowing coverage, as an undiagnosed coexisting bacterial infection could also be present that may not be properly treated with narrower antibiotic coverage. Treatment must continue until both the ANC rises to > 500 cells/μL and an appropriate course of therapy for any specific infection has been completed. If no source of infection is identified (as occurs in ~50% of cases) but the patient defervesces and remains clinically stable, the current regimen of empiric antibiotics should be continued until the ANC rises to > 500 cells/μL. Of note, antibiotics initiated for empiric treatment of resistant gram-positive organisms can be discontinued after 48 hours if such infection is not evident by that time.

Unfortunately, many neutropenic patients experience persistent fevers, and this should prompt a thorough reevaluation of the patient. Of note, it is common practice to continue to draw blood cultures at the time of a subsequent temperature ≥ 38.3° C (101.0° F) a maximum of one time every 24-hour period. Persistent fevers should prompt additional diagnostic testing including cultures, imaging, and testing serum for galactomannan, a fungal wall component, if indicated, as well as broadening antimicrobial coverage. Consideration should be given to the addition of antifungal agents (or to broadening coverage to include molds if the patient is already on antifungal prophylaxis) if fevers continue beyond 4 to 7 days in the absence of a response to antibacterial agents. Patients with either severe neutropenia or a prolonged duration of neutropenia are at high risk for developing infections with *Candida, Aspergillus,* and *Mucor* species. If suspected, CT scans of the chest, abdomen/pelvis, and sinuses may be useful in identifying potential sites of fungal infection. Tissue biopsy is of great utility in confirming a fungal infection, although the procedure indicated to obtain such a specimen may be associated with a high risk of morbidity. In this case, empiric use of antifungal therapy that covers molds such as *Aspergillus* is appropriate and should also be continued until the ANC rises to > 500 cells/μL, the planned course of chemotherapy is completed (if applicable), and resolution of the fungal infection is documented. Neutropenic patients are also prone to developing viral infections, particularly herpes simplex virus (HSV) and cytomegalovirus (CMV) and may require appropriate antiviral therapy. Finally, opportunistic infections such as *Pneumocystis (carinii) jirovecii* pneumonia rarely develop in hospitalized neutropenic patients, but empiric treatment should be considered in the proper clinical scenario such as when steroids or lymphocyte-depleting chemotherapeutic agents are used for at least 1 month without prophylaxis.

ICU providers should seek consultations from both the hematology-oncology and infectious disease services when managing infections in neutropenic cancer patients. In addition to antibiotics used for treatment, many of these patients require antimicrobial prophylaxis against infections that commonly develop during the neutropenic period, and these guidelines should be reviewed in consultation with these specialists.

Neutropenia without Fever

Afebrile neutropenic cancer patients can be managed expectantly (i.e., with observation and monitoring only). As mentioned earlier, these patients may require initiation or continuation of

prophylactic antibiotics. Of course, if an infection is documented even in the absence of fever, it should be treated properly.

The Role of Granulocyte Colony-Stimulating Factors and Granulocyte Transfusions during Neutropenia

The use of granulocyte colony-stimulating factors (CSFs) during the neutropenic period is widely accepted in many scenarios although debatable in others; the data are controversial with regard to efficacy. Therefore, their use in cancer patients in the ICU should be at the discretion of the hematology-oncology consultant with experience in prescribing these agents. However, it would benefit the ICU provider to have a basic understanding of these agents and their indications.

Generally, filgrastim (Neupogen) is the CSF of choice in the hospitalized neutropenic patient. This is dosed on a daily basis at 5 μg/kg subcutaneously and rounded to the nearest of either 300 μg or 480 μg. However, there are instances when sargramostim (Leukine) or pegylated filgrastim (Neulasta) may be chosen instead. When used as primary prophylaxis (i.e., for the prevention of infectious complications in patients anticipated to develop neutropenia as a result of chemotherapy), these agents have been shown to reduce the rates of neutropenic fever and documented infection but with a less clear benefit on short-term infection-related and all-cause mortality. Current guidelines suggest that CSFs should be used for primary prophylaxis in patients receiving chemotherapy regimens for which the anticipated risk of febrile neutropenia is > 20%. However, this varies widely in clinical practice. In general, these agents are administered shortly after the completion of chemotherapy, even if the patient is not neutropenic at that time, and continue until neutropenia has resolved.

It has not been definitively demonstrated that the use of CSFs in the treatment of active neutropenic fever results in prolonged survival. However, a predetermined course of a CSF used for primary prophylaxis of neutropenic fever should be continued if fever develops. In practice, it may very well be appropriate to initiate a CSF at the onset of neutropenic fever in a patient who is critically ill in order to shorten the period of immunosuppression, as the downside of doing so is frequently minimal (potential bone and joint pain and low-grade temperatures).

Finally, granulocyte transfusions from healthy donors are rarely used and should only be considered in patients with severe neutropenia and a life-threatening infection that is unresponsive to antibiotic therapy or in the context of a clinical trial. Respiratory complications including transfusion-related acute lung injury (TRALI) have been reported following granulocyte transfusions (Chapter 46). Although randomized-controlled trials (RCTs) of granulocyte transfusions showed no efficacy when performed several decades ago, another RCT designed to determine the efficacy and safety of granulocyte transfusions in neutropenic patients with bacterial or fungal infections is currently accruing patients at several U.S. centers. It is anticipated that results from this latest RCT may lead to the development of more specific guidelines for the appropriate use of this intervention.

THROMBOCYTOPENIA

The risk of spontaneous bleeding in patients who receive chemotherapy is thought to be greatest when the platelet count falls to < 10,000 cells/μL. Prophylactic platelet transfusions are almost always indicated when the platelet count is within this range. However, some providers will initiate a transfusion at platelet count of < 20,000 cells/μL in the ICU setting. As with nononcologic patients, higher platelet transfusion goals may be required for specific scenarios such as DIC, active bleeding, and invasive procedures including surgery. This threshold should be determined in close collaboration with the consulting hematologist-oncologist and with those performing the intervention (see Table 19.3 in Chapter 19).

Cancer patients, particularly those who have received a significant number of platelet transfusions over their lifetime, are at risk for acquiring *alloantibodies* to platelets. These antibodies are generated by the patient in response to platelet transfusions bearing foreign antigens. Alloantibodies

BOX 24.3 ■ Clinical Pearls in the Management of Neutropenia and Thrombocytopenia in the ICU Cancer Patient

Neutropenic fever is technically defined as a temperature of ≥ 38.0° C (100.4° F) lasting for ≥ 1 hour or an isolated temperature of ≥ 38.3° C (101.0° F) in a patient with an ANC of < 500 cells/μL (although this definition can vary among clinical centers)

Empiric anti-pseudomonal antibiotics (Chapter 18) should be initiated emergently at the onset of neutropenic fever and continued until the ANC is > 500 cells/μL even in the presence of a documented infection treatable with narrower antibiotic therapy

Evaluation for fungal infections should be considered in patients with prolonged neutropenia and recurrent fevers without an identifiable infectious source

In general, in the absence of active bleeding or a planned invasive procedure, the threshold for platelet transfusion should be below 10,000 cells/μL

Failure to achieve a significant rise in platelet count posttransfusion in a patient with a history of multiple platelet transfusions should prompt an evaluation for platelet alloantibodies

are most commonly directed against class I *human leukocyte antigens* (HLA) but may also be directed against epitopes within platelet surface glycoproteins (*human platelet antigens* [HPA]).

Ideally, transfusion of four to six units of random-donor platelets or one unit of single-donor platelets should raise the platelet count by 30,000 to 60,000 platelets/μL. However, when alloantibodies are present, the increase in platelet count posttransfusion is minimal. Many strategies are applied to avoid the acquisition of alloantibodies in cancer patients receiving platelet transfusions, including preferential use of single-donor platelets and reduction of leukocyte transmission using filtration (leukoreduction) or irradiation or both. In addition to reducing the risk of alloimmunization, these latter techniques also reduce the risk of transmission of CMV and transfusion-associated graft versus host disease as well as febrile transfusion reactions (Chapter 46).

In cancer patients demonstrating routinely low platelet counts in spite of transfusion, a CBC should be checked within 30 to 60 minutes of the completion of the platelet transfusion to evaluate for immediate platelet destruction, which suggests the presence of alloantibodies. In this case, the hospital blood bank should be alerted and a test for alloantibodies such as a *panel reactivity antibody* (PRA) assay may be performed. The PRA identifies the presence of anti-HLA antibodies; if present, transfusion of *HLA-matched* platelets may be required in order to achieve appropriate platelet goals. If the PRA is negative but the posttransfusion platelet count supports the presence of alloantibodies, it is possible to request testing for antibodies to common HPA epitopes and *HPA-matched* platelets may be requested.

Measures to treat the underlying cause of thrombocytopenia should be initiated when possible (see Chapters 45 and 63 for more details). In brief, if (nonchemotherapy) drug-induced thrombocytopenia is suspected, offending medications should be discontinued if possible. In the case of suspected or confirmed HIT, alternate anticoagulation should be initiated so long as the platelet count is > 50,000 cells/μL. Immunosuppressive therapy may be warranted if ITP is present. Initial treatment for TTP often includes plasma exchange or the initiation of immunosuppressive therapy, although discontinuation of calcineurin inhibitors may be more appropriate in the case of transplantation-associated thrombotic microangiopathy. Finally, antileukemic therapy with *all-trans retinoic acid* will correct DIC associated with acute promyelocytic leukemia. However, one should also provide transfusion support with platelets to maintain a platelet count > 50,000 cells/μL, cryoprecipitate to maintain a fibrinogen > 150 mg/dL and fresh frozen plasma to maintain an INR < 1.5. These patients require monitoring of the CBCs and coagulation studies (PT/PTT, fibrinogen and D-dimer) every 8 hours until DIC has resolved.

Box 24.3 provides selected clinical pearls related to management of the neutropenic or thrombocytopenic cancer patient in the ICU.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 25

Care of the Challenge-to-Wean Patient

Courtney L. Dostal ■ Aditi Satti ■ Gerard J. Criner

The advancement of intensive care has improved survival for critically ill patients, thereby increasing lengths of stay in the intensive care unit (ICU) and diverse secondary complications. A prolonged ICU stay and chronic critical illness is associated with weakness, deconditioning, and decreased functional status and quality of life. Most ICU patients require mechanical ventilation for an extended period. The process of weaning from mechanical ventilation support may be long and frustrating for patients, their families, and the health care team. A multidisciplinary team approach can emphasize the rehabilitation, medical, and psychosocial issues of the patient and the patient's family and provide a proactive, effective, and comprehensive plan of treatment and care for this common but complex clinical scenario.

Definition

Many studies employed differing definitions of prolonged mechanical ventilation (PMV). For example, the National Association of Medical Director of Respiratory Care (NAMDRC) consensus conference defined chronic ventilatory dependency as receiving mechanical ventilation for at least 6 hours a day for more than 21 days. However, it does not consider a patient ventilator dependent until the acute medical illness causing the respiratory failure has been adequately treated.

Prevalence

The prevalence of patients on PMV varies based on the definition and study population. One international study by Esteban et al examined the survival of 5183 patients on mechanical ventilation from 361 ICUs, observing that 25% of patients received mechanical ventilation for > 7 days. Survival rates also differed based on the patient population. Although the overall mortality rate was 31%, the rate was 52% in patients with the acute respiratory distress syndrome (ARDS) and but only 22% in chronic obstructive pulmonary disease (COPD) patients.

Predicting survival in PMV patients is difficult. In PMV patients in long-term acute care hospitals (LTACHs), Carson and co-workers found that the combination of older age and poor prehospitalization functional status conferred a higher risk of death at 1 year. Other studies revealed a higher incidence of poor functional status and quality of life scores in PMV patients.

Additional online-only material indicated by icon.

Predictors of Weaning Success

The definition of weaning success in PMV is not as clear as in an acute care setting. In an acute setting, extubation within 48 to 72 hours typically defines success. In PMV, there is a slower respiratory recovery time with increased comorbidities. According to the NAMDRC consensus conference, weaning success is defined as removal from mechanical ventilation for 7 consecutive days or a requirement for only nocturnal non-invasive ventilation.

Traditional predictors of weaning are shown in Box 25.1. These parameters predict weaning success in patients ventilated < 7 days, but not in the PMV population. The reason for this discrepancy in predicting outcomes remains unclear. However, it probably relates to the acute-on-chronic respiratory failure affecting most PMV patients with a variety of diverse problems that affect pulmonary, respiratory muscle, and chest wall mechanics.

The poor performance of these traditional weaning parameters has encouraged development of a number of integrated physiologic parameters to predict weaning outcome in the PMV patient population. For example, Gluck et al evaluated a sophisticated scoring system to predict weaning outcome in patients ventilated for 3 weeks. The scoring system, incorporating compliance, resistance, dead space, rapid shallow breathing index, and $PaCO_2$, was more reliable than individual indices. However, this scoring system and similar approaches to predict weaning success in PMV patients have not been validated prospectively. More recently, Verceles et al demonstrated that an improving trend of the rapid shallow breathing index may predict weaning success.

The presence of "good" weaning parameters (traditional or integrated) provides objective support to proceed with weaning, but it does not guarantee a successful outcome or lessen the need for attention to the nonrespiratory factors required to discontinue mechanical ventilation (see Box 25.1). Likewise, "poor" weaning indices should engender caution about progressing and call attention to factors that might compromise the weaning process. However, they should not preclude carefully monitored attempts to begin gradually withdrawing mechanical ventilation.

Factors Associated with Prolonged Mechanical Ventilation

Weakness and deconditioning are widely prevalent in ICU patients requiring mechanical ventilation. Even in healthy persons, a short duration of bed rest adversely effects skeletal muscle performance, with decreased skeletal muscle force by 15% and 20% at days 14 and 35, respectively. Calf and thigh muscle volumes decreased, with a decrease in both slow- and

BOX 25.1 ■ Criteria for Initiating Weaning from Mechanical Ventilation

Original indication for mechanical ventilation resolved or improved
Cardiovascular stability
Neurologic function adequate (spontaneous ventilatory efforts, satisfactory coughing, and swallowing)
Adequate oxygenation ($Pao_2 \geq 60$ mm Hg or O_2 saturation ≥ 90% on $FIO_2 \leq 0.5\%$)
Adequate respiratory mechanics*

* *Defined as one or more of the following: maximal inspiratory pressure more negative than –20 cm H_2O, spontaneous respiratory rate < 35/min, spontaneous tidal volume > 5 mL/kg predicted body weight (PBW), vital capacity > 10 mL/kg PBW, resting minute ventilation ≤ 10 L/min with maximal voluntary ventilation ≥ 2 × resting minute ventilation. (See Chapter 73, Table 73.2, for PBW formulas.)*

FIO_2, fractional concentration of inspired oxygen.

fast-twitch muscle fiber size. Prolonged mechanical ventilation and immobility can weaken the diaphragm, just as occurs in other skeletal muscles. In an animal model, mechanical ventilation for 11 days caused a 25% decrease in maximum transdiaphragmatic pressure and endurance. Correspondingly, diaphragm-biopsy specimens obtained from human subjects on continuous mechanical ventilation for 18 to 69 hours showed atrophy of both slow- and fast-twitch muscle fibers. Diaphragmatic and accessory respiratory muscle weakness contributes to an overall decrease in functional status and impairs weaning from mechanical ventilation.

Neuromuscular weakness is also commonly found in the ICU. Critical illness via associated inflammatory mediators frequently results in critical illness myopathy as well as critical illness neuropathy (Chapter 48). These conditions may be exacerbated by the use of glucocorticoids and neuromuscular blocking agents (Chapter 6). These complications can prolong weaning duration and hospitalization in ICU patients. Although generally reversible, critical illness myopathy and neuropathy require intense and often prolonged rehabilitation.

The weakness and deconditioning that affect respiratory muscles also adversely impact nonrespiratory skeletal muscle of the limbs and oropharynx, and they limit the ability of PMV patients to ambulate, speak, and swallow as well as wean from mechanical ventilation. Multidisciplinary rehabilitation, addressing all of these issues, is required to successfully restore the patient's functional status and ability to wean from PMV.

Factors That Increase Work of Breathing (WOB)

WOB may be increased by processes that raise airway resistance, decrease lung compliance, or stimulate respiratory drive beyond the normal range of minute ventilation (Box 25.2). Lumens of endotracheal tubes acquire an invisible *biofilm* over several weeks of use that markedly increases the tube's airway resistance. Nonetheless, although the timing is debated, placing a tracheostomy tube facilitates weaning by decreasing resistive and elastic loads and thereby the WOB (see Figure 25.E1). This decreased WOB facilitates slow, progressive weans in deconditioned patients with lung mechanics impaired by a chronic underlying disease (e.g., chronic

BOX 25.2 ■ Factors That Increase Work of Breathing

Decreased Lung Compliance
- Abdominal distention
- Intrinsic PEEP (auto-PEEP)
- After lobectomy-pneumonectomy
- Pulmonary edema
- Large pleural effusion
- Supine position

Increased Airway Resistance
- Bronchospasm
- Endotracheal tube (prolonged use)
- Secretions
- Small-diameter tracheal tube
- Ventilator circuit

Increased Respiratory Drive or Minute Ventilation
- End-stage liver or renal disease
- Excessive carbohydrate calories (see Chapter 15)
- Fever, infection
- Metabolic acidosis
- High dead-space to tidal volume ratio (VD/VT) (Appendix B)

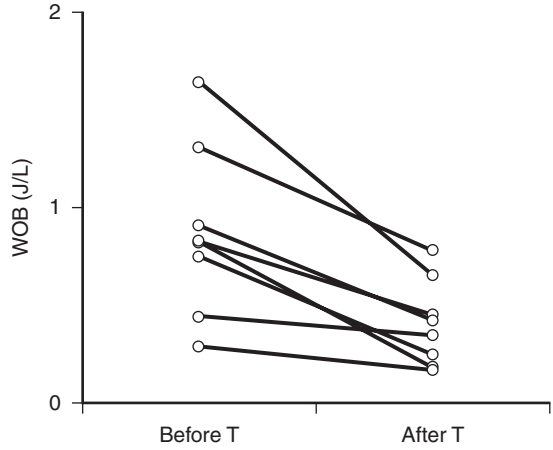


Figure 25.E1 Work of breathing (joules per liter of minute ventilation [J/L]) decreased after tracheostomy. Seven patients had work of breathing (WOB) measured before and after tracheostomy (T) at three identical pressure support levels. Resistive and elastic work, computed from transpulmonary pressure measurements, decreased in all patients after tracheostomy. In addition, three patients with ineffective breathing patterns had improved synchrony after tracheostomy. *(Reproduced with permission from Diehl JL, El Atrous S, Touchard D, et al: Changes in the work of breathing induced by tracheostomy in ventilator dependent patients. Am J Respir Crit Care Med 159:383-389, 1999.)*

obstructive pulmonary disease [COPD]). Other benefits of tracheostomy include easier suctioning, improved patient comfort and mobility, and the potential for earlier initiation of speaking and oral feeding.

The ventilator circuit demand valve also increases airway resistance and thus increases the WOB. Even in assisted modes of ventilation, the WOB may equal or exceed that required for a normal spontaneous breath. Strategies for overcoming the intrinsic ventilator resistance include judicious titration of the flow rate, use of flow-triggered rather than pressure-triggered ventilators, and elimination of breathing circuit dead space.

Mild interstitial pulmonary edema, often unrecognized, may also prolong weaning. The transition from positive pressure ventilation to spontaneous breathing decreases intrathoracic pressures and increases venous return, such that patients with impaired left ventricular function may develop elevated left ventricular diastolic pressure and interstitial pulmonary edema. Also, the stress of weaning may precipitate coronary ischemia, resulting in ischemia-induced left ventricular diastolic dysfunction that further complicates the weaning process.

Rehabilitation in Patients Receiving PMV

Patients with chronic respiratory failure suffer from deconditioning, related to prolonged bed rest and the catabolic nature of their disease. The ability to sit, stand, and ambulate improves functional status and psychological outlook, prevents the complications of immobility, and facilitates weaning (Chapter 21).

Whole-body rehabilitation is an integral part in the care of the PMV patient. One study examined the efficacy of whole-body rehabilitation in 48 chronically ventilated patients. Physical therapy was initiated on admission to the ventilator rehabilitation unit and consisted of trunk control, active and passive extremity resistance training, and inspiratory muscle training. Initially deconditioned and bed-bound patients were able to sit, stand, and ambulate prior to discharge. Also, strengthening the pectoralis muscles, a muscle group of large mass with extensive thoracic attachments and dual inspiratory and expiratory functions, decreased weaning time and improved ventilatory mechanics. The salutary effects of pectoralis strengthening have been documented in other patient populations.

INSPIRATORY MUSCLE TRAINING

Strength training of inspiratory respiratory muscles—using a device with different diameters to provide varying flow and pressure resistance—facilitates weaning. The training program consists of a regular application of increasing resistance for short durations of time. Several studies show favorable effects of daily inspiratory threshold breathing training on inspiratory muscle strength and weaning duration, but have yet to predict greater weaning success.

PSYCHOLOGICAL FACTORS

Psychological factors often significantly prolong weaning (Box 25.3). Cognitive deficits, especially impaired short-term memory, contribute to confusion, miscommunication, and a lack of confidence in self and staff. Contributing factors include the severity of illness, presence of delirium, inability to communicate verbally, prolonged immobility, and sedative medication use. Delirium occurs in up to 80% of patients receiving mechanical ventilation and is most common in elderly ICU patients (Chapter 37).

Trauma patients are particularly prone to psychological disorders from the acute injury and reduced self-esteem from limb loss or other injuries that affect body self-image. Interventions to

BOX 25.3 ■ Psychological and Emotional Factors That Hinder Weaning

Anger	Fear
Anxiety	Isolation
Cognitive deficits	Pain and dyspnea
Depression	Sensory overload
Distorted body image	Sleep deprivation

promote psychological well-being include the use of speech assistive devices, regaining the ability to eat, improved mobility, and repeated staff efforts to reorient the patient to the environment, promote good sleep, and engage them as equal partners in the care plan.

A written schedule for a typical day, easily visible to both the patient and caregivers, provides structure and consistency. A clock, a large-print calendar, and a room with a window help with orientation. Creating a diurnal environment and minimizing nocturnal disruptions can prevent sleep fragmentation and deprivation, which can compromise emotional well-being and impair immunity (Chapter 44). Methods to deal with dyspnea, anxiety, and panic attacks include biofeedback, pursed lip breathing, relaxation techniques, reading, music, prayer, television viewing, and portable fans to blow air on the patient's face. Air blowing stimulates afferent cutaneous nerves that reflexively inhibit the sensation of dyspnea.

Speech therapists are an integral part of the multidisciplinary team (see Table 21.1 in Chapter 21). A one-way speaking valve or electrolarynx can assist patient speech, despite the presence of a tracheostomy. Speech therapists also evaluate swallowing, oral motor strength, and the presence of adequate cough and gag reflexes (Chapter 22). The PMV patient population has a high incidence of aspiration, and a modified barium swallow study with videofluoroscopy (or fiberoptic endoscopic evaluation of swallowing [FEES] [Chapter 22]) can identify these patients. The ability to eat, speak, and socially interact reengages the patient in normal human behavior and is vital to the patient's well-being. A complete rehabilitation program improves overall functional status and facilitates weaning from the ventilator.

Specialized Patient Populations Receiving PMV

COPD

Respiratory failure in a COPD patient is an ominous sign and portends a high morbidity and mortality (Chapter 76). The patient with COPD may have difficulty weaning for a number of reasons. COPD patients develop hyperinflation (elevated end-expiratory lung volume), or intrinsic positive end-expiratory pressure (auto-PEEP). The adverse effects of hyperinflation include increased WOB, dyspnea, hypotension, and failure to wean. Auto-PEEP can cause patient-ventilator asynchrony and increase WOB because the patient's initial inspiratory effort is insufficient to trigger the ventilator (this occurs because these patients have to create a pressure above their auto-PEEP level in order for the ventilator to detect their inspiratory effort). Treatment of expiratory flow limitation (bronchospasm), adjustments in the flow rate and inspiratory:expiratory ratio, or the addition of external PEEP (to just below the level of auto-PEEP) can address this problem.

Both nebulizers and metered dose inhalers (MDIs) can effectively deliver bronchodilator aerosols to the lower respiratory tract. Patients with COPD may require higher doses of bronchodilators, with a significant decrease in airway resistance seen with doses of albuterol up to 7.5 mg.

Another aspect to consider in hypercapnic COPD patients is to avoid overcorrecting the $PaCO_2$ to a value below the patient's baseline (see Appendix B). Such overcorrection causes excessive renal excretion of bicarbonate. Then, when these patients resume their usual level of reduced spontaneous minute ventilation and the $PaCO_2$ rises, inadequate buffering exists to maintain the normal range of pH. Patients experience excessive breathlessness and cannot successfully wean.

Also, one must carefully address nutritional needs. Excess carbohydrate calories can produce a respiratory quotient (RQ) > 1, with increased CO_2 production, minute ventilation, and WOB. Conversely, malnutrition diminishes respiratory muscle strength and endurance, thereby limiting weaning. Tracheostomies can lead to dysphagia and cause vocal cord dysfunction. Patients with tracheostomies may require diets of altered consistencies to reduce aspiration.

Some patients with COPD fail to wean. In this circumstance, unusual techniques may be considered. For example, transtracheal administration of continuous, high flow, heated, humidified oxygen may assist in ventilation by decreasing dead space ventilation, dynamic hyperinflation, respiratory rate, minute ventilation, and $PaCO_2$ in chronic respiratory failure patients.

Lung volume reduction surgery (LVRS) may also benefit emphysematous COPD patients who are unable to wean. In one small study, three patients underwent LVRS after failing aggressive medical therapy and mechanical ventilation for 11 to 16 weeks. Postoperative improvements in oxygenation, reduction in $PaCO_2$, and improvement in pulmonary mechanics enabled successful weaning from the ventilator. These therapeutic options could be considered in COPD patients who remain unweanable despite aggressive medical therapy.

RESTRICTIVE LUNG DISEASE

Chest wall deformities, obesity, and neuromuscular disease are all restrictive lung disorders that can present a challenge to wean. These patients have decreased total lung volumes and functional residual capacities. In patients with neuromuscular disease, diminished muscle strength leads to a rapid, shallow breathing pattern and increased WOB (Chapter 1). Abnormalities in gas exchange can occur when inspiratory muscle strength decreases to 30% of normal. Weakness in expiratory strength can limit cough and secretion clearance, leading to atelectasis.

Most patients with restrictive lung disease also have evidence of sleep-disordered breathing, presenting as apneas, oxygen desaturations, hypoventilation, and sleep fragmentation. Sleep-disordered breathing with hypoventilation and desaturations is more frequent during rapid eye movement (REM) sleep, because of the loss of diaphragmatic and accessory respiratory muscle tone in REM sleep. Chronic nocturnal hypoventilation can eventually lead to daytime hypercapnia. Pulmonary hypertension may occur as a result of pulmonary vascular remodeling and vasoconstriction from alveolar hypoxia or sustained hypercapnia. These patients are good candidates for chronic intermittent nocturnal ventilation.

CHEST WALL DISORDERS

Idiopathic scoliosis or the sequelae of tuberculosis can lead to chest wall deformities. Scoliosis is a lateral curvature of the spine. The scoliotic angle (degree of spine curvature) correlates to the severity of restriction in pulmonary function. In one group, 24 patients with untreated scoliosis were followed for 20 years to determine the progression of their lung disease. In these untreated patients, a spine angulation of more than 100 degrees and vital capacity < 45% of predicted portended a poorer prognosis and higher likelihood of respiratory failure.

Chronic intermittent nocturnal ventilation can reverse the sequelae of cor pulmonale in severe kyphoscoliosis within 6 weeks of initiating therapy. Survival studies in patients with chest wall disorders reveal improved survival in those treated with invasive or non-invasive ventilation.

NEUROMUSCULAR DISORDERS

Neuromuscular disorders may lead to respiratory failure. Poliomyelitis, myopathies, and amyotrophic lateral sclerosis (ALS) are all neuromuscular disorders affecting the lower motor neuron unit. Examples of upper motor neuron disease include stroke and Parkinson's disease. Spinal cord injuries may produce upper and/or lower motor neuron deficits. The severity of respiratory weakness depends on the level of neuromuscular impairment.

Depending on the stroke location, the patient may develop Cheyne-Stokes respiration, or alternating hyper- and hypoventilation. High spinal cord injuries (C_1-C_3) typically require mechanical ventilation. Lower spinal cord injuries may result in respiratory muscle weakness and abnormal thoracoabdominal movement, which is worse in the supine position. The acutely reduced vital capacity after spinal cord injury may improve over extended periods of time. Patients with Parkinson's disease have dysfunction of their glottic muscles causing upper airway obstruction and aspirations. Treatment of the underlying Parkinson's disease may improve respiratory muscle function.

Multiple sclerosis, a central nervous system demyelinating disorder, can cause respiratory muscle weakness and bulbar dysfunction that are notably worsened when the patients become febrile. These patients experience a decrease in maximum inspiratory and expiratory pressures with time and lose their ability to cough and swallow, thereby predisposing them to respiratory infections and aspiration. Respiratory muscle training may improve their pulmonary function.

ALS is a lower motor neuron disease, culminating in eventual respiratory failure. The sniff nasal inspiratory force (SNIF) test can predict survival in ALS, with a SNIF between 0 and −40 cm H_2O predicting a 6-month median survival of 50%. The use of non-invasive ventilation improves survival in patients with ALS and no bulbar involvement, and it may be especially beneficial in rapidly progressing patients.

Treatments

LONG-TERM OXYGEN THERAPY

Patients with neuromuscular disease may exhibit chronic hypercapnia. The use of low-flow continuous oxygen may further raise $PaCO_2$ and is not recommended in patients except when they have concomitant hypoxemia. However, the use of long-term ventilation is associated with an improved survival compared to oxygen alone in patients with chest wall dysfunction.

LONG-TERM MECHANICAL VENTILATION

The indications for long-term ventilation are listed in Box 25.4. Patients should be cooperative, medically stable, and without contraindications for non-invasive mechanical ventilation (Chapter 3). If non-invasive ventilation attempts fail, a tracheostomy can be placed and invasive mechanical ventilation initiated. Discharge arrangements include home equipment, tracheostomy care, and home respiratory therapy.

In patients with restrictive disorders, patient comfort should be emphasized. Appropriate settings can be determined in the hospital, with a quiet, inexpensive, simple, and lightweight ventilator chosen. Patients should be started with low inflation pressures, which are gradually increased, allowing patients time to adapt. Inspiratory pressures in non-invasive ventilation can be gradually increased up to 20 cm H_2O in patients with neuromuscular disease if necessary, and even higher in patients with chest wall dysfunction. Patients do not usually develop auto-PEEP and the expiratory positive airway pressure (EPAP) can be set at a minimal level (Chapter 3). If a volume-limited ventilator is chosen, a respiratory rate close to the patient's spontaneous breathing rate should be set with a tidal volume of 10 mL/kg predicted body weight (PBW). Adjustments to settings

BOX 25.4 ■ Indications for Non-invasive Ventilation

Symptoms consistent with sleep disruption or hypoventilation
Daytime hypoventilation: $PaCO_2$ > 45 mm Hg
Nocturnal hypoventilation: O_2 sat < 88% for > 5 min
Severe restrictive ventilation: FVC < 50% predicted
Repeated hospitalizations for respiratory exacerbations

FVC, forced vital capacity.

should be made based on the patient's symptoms and functional status, with guidance from occasional daytime $PaCO_2$ results. These patients may also benefit from inspiratory muscle training to increase respiratory muscle strength. The goal for these patients is to achieve the highest level of functioning with rehabilitation and ventilator settings that are comfortable for the patient.

Obesity

Obesity is frequently encountered in the ICU and increases the risk of morbidity and mortality (Chapters 29 and 80). The duration of mechanical ventilation, oxygen requirement, and hospital stay is higher for obese than for non-obese patients. Obesity can pose difficulties with airway management and weaning from the ventilator. Risk factors for a difficult intubation in obese patients include a high Mallampati score, large neck circumference, and limited neck mobility, and they should engender preparations to secure an adequate airway in this situation.

An increase in body mass index (BMI) to the range of morbid obesity typically leads to a drop in forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), total lung capacity (TLC), functional residual capacity (FRC), and expiratory reserve volume. Obese patients have decreased chest wall compliance and low lung volumes leading to an increased WOB. When initiating mechanical ventilation, one should set the initial tidal volume based on predicted, not actual, body weight, to avoid high pressures, alveolar overdistention, and barotrauma. Poor oxygenation and $\dot{V}/\dot{Q}$ mismatch can be due to atelectasis, and therapeutic application of PEEP may be beneficial. Early application of 10 cm of PEEP improves oxygenation, lung volumes and prevents alveolar collapse. Consider early tracheostomy in obese patients with respiratory failure, but recognize that this procedure can be technically challenging because of the cervical anatomy and increased neck girth. Extra-long tracheostomy tubes (designated as *proximal extra long* or *proximal XL-tubes*) should be used to span the pretracheal tissue (Chapter 22).

Supine positioning can worsen oxygenation by increasing $\dot{V}/\dot{Q}$ mismatch and decreasing FRC further. Placement of obese patients in the reverse Trendelenburg position at 45 degrees or more can facilitate weaning by decreasing minute ventilation (increased tidal volume and decreased respiratory rate). Such semi-upright to upright positioning also takes into account the higher incidence of hiatal hernia and aspiration from the increased abdominal pressure. Preventive measures to suppress acid aspiration should be taken.

Postcardiac Surgery Patients

Congestive heart failure, related to preoperative left ventricular dysfunction or unsuccessful revascularization, is common and prolongs weaning. Also, diaphragmatic dysfunction (confirmed by electromyography) occurs in up to 10% of patients following coronary artery bypass surgery and may persist for months. This dysfunction is commonly due to phrenic nerve injury from ice slush topical cardioplegia, surgical trauma, and ischemia from the use of the internal mammary artery

as a vascular conduit. Interventions include sitting in an erect position to facilitate diaphragmatic excursion that, in turn, can prevent or reverse atelectasis. Furthermore, the patient with a recent myocardial infarction should be weaned cautiously. These individuals may benefit from a pressure support wean rather than a T-piece wean (discussed later), allowing gradual cardiovascular adjustment to the increased demands of breathing, with fewer dramatic shifts in both pleural pressures and venous return to the right atrium.

Choice of Weaning Techniques

An important decision is the choice of weaning technique. Weaning modalities gradually shift the WOB from the ventilator to the patient (see Chapter 4). Traditional weaning methods involve (1) increasing periods of spontaneous breathing, alternating with rest modes of full ventilatory support (T-piece or continuous positive airway pressure [CPAP] wean) and (2) gradual removal of the support provided to each breath (pressure support wean).

Weaning can be viewed as a process of respiratory muscle training and reconditioning. From this perspective, T-piece weaning aims to strengthen respiratory muscles; and pressure support weaning promotes respiratory muscle endurance. Regardless of the technique employed, the goal is to recondition of the respiratory muscles without inducing fatigue.

Studies comparing the efficacy of these techniques have yielded conflicting results, with no single approach clearly superior for the majority of chronically ventilator-dependent patients. Consequently, the decision regarding the initial weaning modality remains determined by the clinician's experience and the patient's characteristics. At the start of the process, regardless of the approach, one should perform weaning during the day rather than at night. At night, the respiratory muscles should be unloaded (i.e., rested). One should not push the patient to obvious respiratory muscle fatigue, with evidence of respiratory paradox or severe respiratory distress. Although the optimal interval of rest remains unknown, providing adequate rest, as well as adequate nutrition, is crucial. The clinician must be open and flexible to alternative strategies if the initial approach is unsuccessful.

Lack of Progress in Weaning

Many patients fail to make progress initially, despite meticulous and appropriate care. In this circumstance, the ICU team needs to maintain patience and focus. The team should continuously reevaluate the patient for factors that interfere with weaning and employ alternative weaning strategies. Although some individuals will never achieve complete liberation from ventilatory support, many will with time and patience.

Options for the Persistently Ventilator-Dependent Patient

Depending on the geographic region, transfer to a specialized subacute care facility (see Chapter 109) that specializes in chronic respiratory care or weaning may be an option for patients failing to progress in an acute care setting. These facilities provide a focused, multidisciplinary, consistent approach to weaning management. As studies have demonstrated, facilities have a positive impact on cost and patient outcome.

Some patients, despite best efforts, may never achieve complete independence from positive pressure mechanical ventilation. The patient with severe neuromuscular disease, high spinal cord injury, or advanced pulmonary disease may require partial or alternative ventilatory support, such as nocturnal positive pressure ventilation, non-invasive ventilation, or negative pressure ventilation. For these patients, subacute or chronic ventilator units in long-term care facilities or home ventilation may be reasonable options. The cost of care in these facilities is one fourth to one third the cost

of ICU care. Discharge to home on a portable ventilator is feasible for the patient with a dedicated family support system, following appropriate training for both the patient and the family. Numerous studies demonstrate that home mechanical ventilation improves a patient's quality of life.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 26

Care of the Patient with End-Stage Renal Disease

Alan G. Wasserstein ■ Melissa B. Bleicher

End-stage renal disease (ESRD) or stage 5 chronic kidney disease (CKD) and its treatment influence virtually every aspect of critical care in affected patients. ESRD designates advanced renal failure in which hemodialysis (HD), peritoneal dialysis (PD), or a renal allograft is required to ameliorate symptoms and prolong life. Stage 5 CKD designates estimated glomerular filtration rate (eGFR) below 15 mL/min/1.73 sq-m. However, dialysis does not completely correct the complex derangements of uremia, whereas both dialysis and immunosuppressive treatment for renal transplantation introduce additional risks of their own.

Common Problems in Patients with End-Stage Renal Disease in the Intensive Care Unit

Some aspects of ESRD contribute to the genesis of critical illnesses, whereas others complicate their management (Box 26.1).

CARDIOVASCULAR COMPLICATIONS

Fluid overload resulting from patient noncompliance with regular dialysis or from iatrogenic fluid administration should be distinguished from primary heart failure by echocardiography. Left ventricular hypertrophy is extremely common in dialysis patients, resulting primarily from chronic hypertension. It progresses to *diastolic dysfunction* (reduced left ventricular compliance) and ultimately to dilated cardiomyopathy with systolic dysfunction and hypotension.

Systolic dysfunction is rarely exacerbated by placement of an arteriovenous (AV) fistula (usually an upper arm fistula between the brachial artery and vein). Bradycardia during transient occlusion of an AV fistula is a specific but not sensitive marker of high-output heart failure (Branham sign) (but is not recommended due to associated risk of clotting off the fistula). *Hypotension* complicates HD treatments in hemodynamically unstable intensive care unit (ICU) patients as well as in patients undergoing routine outpatient dialysis. Hypotension occurs in part because the normal homeostatic response to fluid removal—namely, vasoconstriction—is impaired during HD. Hypotension, in turn, may result in vascular access thrombosis, usually in association with underlying stenosis of the venous anastomosis (Box 26.2).

Pulmonary edema may result from fluid overload, an episode of accelerated hypertension, or myocardial infarction, all of which are often superimposed on prior left ventricular dysfunction. Patients sometimes present with pulmonary edema caused by occult fluid overload. In these circumstances, the patient's body weight is maintained by fluid accumulation, and the loss of lean body mass is not recognized during outpatient care. *Coronary artery disease*, a common cause of death in patients with ESRD, is due to diverse "nontraditional" metabolic

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BOX 26.1 ■ Common Problems in Patients with End-Stage Renal Disease in the ICU

Cardiovascular

Fluid overload with high volume intravenous fluid therapy
Left ventricular failure resulting from systolic and diastolic dysfunction
Coronary ischemia and ischemia-induced arrhythmias
Dialysis-induced hypotension

Hematologic

Anemia
Bleeding caused by platelet dysfunction

Infection

Increased bacterial infections, especially at sites of dialysis access

Gastrointestinal

Bowel ischemia or obstruction
Gastroduodenitis
Pancreatitis

Neurologic

Encephalopathy
Seizures
Opioid sensitivity

Electrolyte Derangements

Hyponatremia
Hyper- and hypokalemia

Drug Dosing Problems

Excessive dosage
Inadequate dosage

BOX 26.2 ■ Treatment of Vascular Access Thrombosis

Perform emergency dialysis if necessary through a temporary venous catheter
Clot is removed by surgical thrombectomy or by mechanical (wire) thrombolysis, usually by interventional radiologists; avoid thrombolytics if there is a bleeding risk
Thrombosed central venous catheters are treated by thrombolytic instillation or by catheter replacement
After thrombectomy or thrombolysis, fistulography should be performed to detect an underlying vascular access stenosis

abnormalities associated with uremia, including specific lipid abnormalities, vascular calcification, inflammatory mediators and advanced glycosylation end products, and endothelial dysfunction.

Pericarditis may precede the initiation of maintenance dialysis or it may occur in chronic dialysis patients. The incidence of uremic pericarditis has significantly decreased as standard practice has shifted toward earlier initiation and more intensive dialysis. Patients with poor adherence to prescribed treatment, or those with access malfunction, remain at risk. In addition, patients with ESRD secondary to autoimmune diseases like lupus or rheumatoid arthritis may develop a flare with serositis and effusions. Finally, antihypertensive medications including hydralazine or minoxidil may cause a lupus-like syndrome or hemorrhagic pericarditis, respectively.

Arrhythmias are the most common cause of cardiac death in the dialysis population and most likely when nearing the end of a 72-hour dialysis-free "weekend" obligated by the thrice weekly outpatient hemodialysis schedule. Arrhythmias are also exacerbated by dialysis against inappropriately low dialysate potassium concentrations.

PULMONARY COMPLICATIONS

Uremic lung refers to putative increased pulmonary capillary leakiness in patients with ESRD. Clinical confirmation of this entity is lacking, and it may be due entirely to volume overload. *Pleural effusion* may be due to fluid overload, uremic serositis, tuberculosis (from an increased incidence of reactivation of tuberculosis in ESRD patients), or diaphragmatic leak associated with PD. *Dyspnea during dialysis* can be due to dialysis-induced hypoxemia, which is generally modest (i.e., a reduction of Pao_2 of 10 to 15 mm Hg) but can be problematic in patients with chronic lung disease. Dyspnea can also be due to an anaphylactoid reaction to the dialyzer. Peritoneal dialysis fluid can elevate the diaphragm, especially when the patient is supine, and compromise ventilation in patients with pulmonary disease. *Sleep apnea syndrome* occurs in 40% of patients with ESRD. These patients have an increased sensitivity to drugs that worsen their sleep-disordered breathing and cause respiratory depression. Sirolimus, an immunosuppressant, may cause hemorrhagic pneumonitis, which may manifest as diffuse alveolar hemorrhage.

HEMATOLOGIC COMPLICATIONS

The *anemia* of ESRD is mainly due to deficiency of kidney-produced erythropoietin. Full response to recombinant erythropoietin requires 4 to 8 weeks, and therefore cannot correct anemia in the acutely ill patient. In addition, inflammation, infection, and even minor surgery blunt the normal marrow response to erythropoietin to a remarkable degree. *Uremic bleeding* is due to a functional defect in von Willebrand factor, inhibition of adenosine diphosphate (ADP)-induced platelet aggregation, and anemia. Measurement of bleeding time can quantify bleeding risk, but its predictive power is limited for any individual patient. Although inadequate dialysis can prolong the bleeding time, intensive dialysis may not fully correct it. Anemia also increases bleeding time because of a rheologic mechanism: at a hematocrit of less than 30%, platelets stream in the center of blood vessels away from the vessel wall.

INFECTIOUS COMPLICATIONS

Dialysis patients receiving *chronic dialysis* have decreased host defenses. Impaired granulocyte functions include chemotaxis, phagocytosis, and intracellular killing. Impaired lymphocyte functions include defective antibody production and inadequate response to vaccines. These defects result from both the uremic state and exposure to bioincompatible dialysis membranes. Bioincompatibility connotes complement activation and cytokine release stimulated by exposure to the dialysis membrane. These changes in granulocyte and lymphocyte function in dialysis patients manifest as increased susceptibility to common bacterial pathogens rather than to opportunistic pathogens (e.g., *Pneumocystis jiroveci*). Infectious risk in renal transplant recipients varies with time after transplant, influencing both intensity of immunosuppression and use of prophylactic strategies. In the earliest postoperative period, donor-derived and nosocomial infections are of greatest concern, whereas in the late posttransplant period, community-acquired infections predominate.

Infected vascular access sites, especially central venous catheters, are the leading cause of bacteremia in dialysis patients. Offending organisms are usually staphylococci and streptococci but may include gram-negative rods. PD patients suffer from catheter-associated peritonitis, characterized by bouts of abdominal pain, an elevated peritoneal fluid white blood cell count (> 100 cells/μL),

cloudy effluent, and positive peritoneal fluid cultures with the same spectrum of pathogens as affect hemodialysis catheters. Tunneling of the dialysis catheter, meticulous catheter care, and local antibiotic at the exit site reduce infectious risk. Urinary tract infections are also common in dialysis patients and may occur even if urine output is minimal.

NEUROLOGIC COMPLICATIONS

Uremic encephalopathy causes somnolence, confusion, seizures, and coma. Physical signs include hyperreflexia, asterixis, and myoclonus. Patients on maintenance HD may have unrecognized uremic encephalopathy resulting from access malfunction or noncompliance. Severe elevation of blood urea nitrogen (BUN), which may be due to bleeding, catabolism, or total parenteral nutrition (TPN), has no effect on neurologic function and is not by itself an indicator of uremic encephalopathy. Alterations in mental status may respond to intensive dialysis. *Subdural hematomas* may be spontaneous rather than traumatic. Both uremic platelet dysfunction and exposure to heparin during HD may contribute. Because active metabolites of morphine or meperidine accumulate in renal failure (the latter causes seizures), their use should be avoided. Hydromorphone and fentanyl are preferred analgesics in ESRD. Renal transplant recipients are at increased risk of infectious neurologic complications including meningitis and encephalitis, as well as medication-induced posterior leukoencephalopathy.

GASTROINTESTINAL COMPLICATIONS

Dialysis patients have a high incidence of gastritis and nodular duodenitis. The incidence of peptic ulcer disease caused by *Helicobacter pylori* is not increased. Upper gastrointestinal bleeding is usually due to superficial mucosal lesions (often drug-induced) or arteriovenous malformations (AVMs) rather than to gastric or duodenal ulcers. Pancreatitis is more common in ESRD patients than in nonuremic patients, possibly because of pancreatic calcification.

ELECTROLYTE AND ACID-BASE COMPLICATIONS

Renal excretion of fixed acid, compensation for respiratory alkalosis or acidosis, and elimination of excess administered alkali are all absent in ESRD. Although dialysis provides alkali as bicarbonate (HD) or lactate (PD) to neutralize fixed acid, ESRD patients characteristically have an elevated anion gap (16 to 20 mEq/L). An anion gap greater than 25 mEq/L suggests an additional cause of acidosis (see Chapters 82 and 83). Because dialysis removes excess salt and fluid, intravenous sodium bicarbonate can be given to treat metabolic acidosis.

Hyponatremia is common in dialysis patients in the ICU because of the administration of large volumes of hypotonic fluids in the absence of renal water excretion. *Hypokalemia* may be due to malnutrition or to the use of total parenteral nutrition (TPN) (because glucose in TPN drives potassium into cells). Hypokalemia is also common in apparently well-nourished PD patients. Dialysate potassium levels must be adjusted upward to avoid hypokalemia, particularly in patients receiving digitalis. *Hyperkalemia* is treated by dialysis, although one may temporize with intravenous calcium, insulin and glucose, and potassium-binding resins (see Chapter 39). Sodium bicarbonate infusion to reverse hyperkalemia is ineffective in dialysis patients.

NUTRITIONAL COMPLICATIONS

As a rule, dialysis patients have baseline malnutrition caused by poor food intake, increased protein losses related to dialysis, and catabolism. Dialysis-related protein losses increase concurrently with greater cumulative frequency or intensity of dialysis provided during critical illness. Patients

with ESRD are predisposed to catabolism by inflammatory mediators and by the hemodialysis procedure itself, which increases catabolic cytokines, such as interleukin-1 and tumor necrosis factor. Malnutrition increases the risk for infection. Hence, nutritional therapy for malnutrition is indicated early in the ICU course of patients with ESRD (see Chapter 15).

Diagnostic Considerations

Differential diagnoses of common problems in ICU patients are influenced by ESRD (Table 26.1). In addition, the manifestations of disease may be altered by ESRD. For example, fever may be less marked for a number of reasons, such as the use of steroid treatment in the renal transplant patient.

Knowing the cause of ESRD may also be useful—for example, if ESRD is due to polycystic kidney disease, diabetes, or lupus. Associations with polycystic kidney disease include cerebral aneurysms, prolapsed mitral valve, diverticulitis, kidney stones, hernias, and infected or bleeding renal cysts.

With thrombocytopenia, heparin antibodies should be sought (see Chapter 45), although the incidence of heparin-induced thrombocytopenia is much lower in ESRD than in the general population. In patients with ESRD and fever, infections of their vascular access and urinary tract should be particularly suspected. Dialysis catheter exit site infection is distinguished by discharge at the exit site and tunnel infection by redness and tenderness along the subcutaneous tunnel. However, catheter-associated bacteremia typically occurs without external evidence of infection.

Serum enzyme levels may be altered in ESRD. For example, in ESRD without pancreatitis, serum amylase may be elevated up to three times normal levels and lipase to twice normal levels. Greater elevations than these suggest pancreatitis. Creatine kinase, including the MB fraction, is persistently elevated in 10% to 50% of dialysis patients. Elevation of cardiac troponin T in the absence of cardiac symptoms is very common in the ESRD population and therefore unreliable in the diagnosis of acute myocardial infarction. However, increased troponin T significantly predicts

TABLE 26.1 ■ **Differential Diagnosis of Common Problems in Patients with End-Stage Renal Disease in the ICU**

Problem	Differential Diagnosis
Chest pain	Coronary artery disease
	Gastroesophageal reflux disease
	Pericarditis
	Uremic pleurisy
	Dialyzer reaction
Bleeding	Uremia
	Platelet defect
	Heparin overdose
	Heparin-induced thrombocytopenia
Fever	Infection of vascular access
	Urinary tract infection
	Opportunistic infections in renal transplant patients
Obtundation	Uremia
	Opioids or other sedatives
	Sepsis syndrome
	Malignant hypertension
	Subdural hematoma or other intracranial bleeding
	Central nervous system lymphoma in renal transplant patients

mortality, cardiovascular outcomes, and noncardiovascular death in this population. Cardiac troponin I is a sensitive and specific marker of myocardial injury, even in ESRD (see Chapter 50).

Management

CARDIOVASCULAR PROBLEMS

As a rule, avoid excessive fluid administration, but critically ill patients often require large amounts of crystalloid to maintain hemodynamic stability in the face of increased capillary permeability (so-called third spacing), as well as TPN, multiple antibiotics, and other infusions. In these circumstances, perform dialysis more frequently to minimize fluid overload, particularly as third-space fluid is mobilized. Dialytic support of the hemodynamically unstable patient can be achieved by increasing the frequency of dialysis, slowing the rate of fluid removal, using hypertonic dialysate, reducing dialysate temperature, using high calcium dialysate, performing isolated ultrafiltration without dialysis, providing vasopressor support, and using continuous renal replacement therapy (venovenous hemodialysis or hemodiafiltration) (see Chapter 20). Adequate preload is usually critical for maintaining cardiac output in patients with diastolic dysfunction, so avoid excessively rapid fluid removal in these patients. In PD, fluid removal requires an increase in frequency or tonicity of exchanges. If the PD patient has respiratory embarrassment, decrease exchange volume (e.g., to 1 L) and increase the frequency of exchanges.

In *angina* or *myocardial infarction* in ESRD, correct anemia with blood transfusion rather than erythropoietin. Percutaneous transluminal angioplasty for coronary artery disease is limited by increased rates of restenosis in ESRD, but surgical revascularization has a higher mortality than in nonuremic patients. In management of *arrhythmias,* avoid *hypokalemia*, especially in patients receiving digitalis. Amiodarone is preferred to procainamide, whose active metabolite (N-acetylprocainamide, or NAPA) may accumulate to dangerous levels in renal failure.

In *uremic pericarditis,* nonsteroidal anti-inflammatory drugs do not alter natural history or alleviate pain. Treat moderate-size or symptomatic pericardial effusions with intensive dialysis, monitored closely by echocardiography. Large pericardial effusions (≥ 250 mL or > 1 cm posterior echo-free space) or pericardial tamponades require drainage. Retrospective case series suggest poorer outcomes with pericardiocentesis compared with pericardiectomy or pericardiotomy in the dialysis-dependent population.

Treat *bleeding problems* by blood transfusion to achieve a hematocrit greater than 30% and by other measures (Table 26.2). Platelet transfusions are of limited value because transfused platelets quickly become dysfunctional in the uremic milieu. Reserve their use as a therapy of last resort for patients with life-threatening active bleeding who have not responded to the other measures listed in Table 26.2.

INFECTIOUS PROBLEMS

Infections are treated empirically with an antistaphylococcal agent (e.g., vancomycin to cover methicillin-resistant staphylococcal [MRSA] species) and a third-generation cephalosporin or aminoglycoside pending cultures (see Chapters 17 and 18). Prolonged aminoglycoside use in ESRD risks eighth cranial nerve toxicity (deafness or ataxia). Therefore, carefully monitor trough levels, limit the course of therapy, and if possible, use an alternative antibiotic. Central venous dialysis access catheters usually should be suspected as an infectious source during otherwise unexplained fever associated with sepsis, or bacteremia, and removed (see Chapter 14). Tunneled dialysis catheters may be exchanged over a wire (instead of removed) in patients with bacteremia who appear nontoxic and whose vascular access sites are especially limited. AV grafts should be observed closely and removed surgically if they manifest local signs of infection. In contrast, AV fistulas can usually be treated successfully with antibiotics without surgical intervention.

TABLE 26.2 ■ **Treatment of Bleeding in Patients with End-Stage Renal Disease in the Intensive Care Unit**

Treatment	Dosage	Onset	Duration	Comment
Raise Hct to 30% by red blood cell transfusion	Variable	Immediate	Variable	Rheologic mechanism
Increase intensity or frequency of dialysis or both	—	5–7 days	—	Variable benefit
Desmopressin (DDAVP)	0.3 μg/kg (IV over 20–30 min)	1 h	6–8 h	Increases circulating endogenous von Willebrand factor (VWF); tachyphylaxis after one to two doses
Conjugated estrogens	0.6 mg/kg (IV once a day for 5 days)	6 h–2 days	14–21 days	No adverse effects
Cryoprecipitate*	10 units IV	1 h	24–36 h	Carries an infectious risk; provides exogenous von Willebrand factor
Platelet transfusion†	6 units IV	Immediate	Variable	Carries risks of transfusion reactions

*Because of its significant infectious risk, cryoprecipitate should be restricted to treatment of life-threatening active bleeding not responding to other interventions listed.
†Because transfused platelets become dysfunctional in a short period of time in uremic patients, they should only be given for active life-threatening bleeding that has not responded to the other measures listed in the table.
Hct, hematocrit; DDAVP, deamino-8-D-arginine vasopressin (desmopressin); IV, intravenous.

Drug dosing in patients with impaired renal function has traditionally been based on the Cockcroft-Gault equation for estimating creatinine clearance (CrCl). Of late, the nephrology community has utilized the modification of diet in renal disease (MDRD) equation for estimating renal function, and laboratories now often report these estimates along with serum chemistry results. However, the Cockcroft-Gault equation is preferred for drug dosing, since use of the MDRD-derived eGFR will overdose patients with stages 4 and 5 CKD but underdose patients with stage 3 CKD. *Dosing in patients on dialysis* will vary with the frequency and intensity of renal replacement therapy. Pharmacokinetic-based recommendations for antibiotics that require dose modification for continuous as well as intermittent hemodialysis are included in Table 26.E1. In the renal *transplant recipient*, take care to assess for interactions between antibiotics and metabolism of immunosuppressant medications mediated through the cytochrome P450 system.

NUTRITIONAL PROBLEMS

Most critically ill ICU patients with ESRD require enteral nutrition or TPN. Use of 70% dextrose solutions minimizes the volume of administered water. In general, the daily protein goal should be 1.5 g/kg/d (see Chapter 15). Protein supplementation above this limit typically increases generation of uremic toxins without increasing anabolism. Phosphate, potassium, and magnesium should initially be added to the TPN solutions in normal quantities (unless their serum levels are already high) because these minerals may be shifted into cells by glucose infusion and anabolism. Monitor these electrolytes regularly and adjust their supplementation on a daily basis.

TABLE 26.E1 ■ **Dosing of Antimicrobial Agents during Renal Replacement Therapy***

Class	Drug	Loading Dose	CVVH	CVVHD	CVVHDF	Intermittent HD
Aminoglycoside	Amikacin	10 mg/kg	7.5 mg/kg q24–48h	Same	Same	5–7.5 mg/kg q48–72h
	Gentamicin Tobramycin	2–3 mg/kg	1–2.5 mg/kg q24h	Same	Same	1–2.5 mg/kg q48–72h
Azoles	Fluconazole	400–800 mg	200–400 mg q24h	400–800 mg q24h	800 mg q24h	100–200 mg q24h or 200–400 mg q48–72h
	Itraconazole	None	200 mg q12x4 then 200 mg q24h	Same	Same	Same
	Voriconazole	400 mg PO q12x2	20 mg PO q12h	Same	Same	Same
Carbapenems	Imipenem	1 g	500 mg q8h	500 mg q6–8h	500 mg q6h	250–500 mg q12h
	Meropenem	1 g	0.5–1 g q12h	0.5–1 g q8–12h	0.5–1 g q8–12h	500 mg q24h
Cephalosporin	Cefazolin	2 g	1–2 g q12h	1 g q8h or 2 g q12h	Same	500–1000 mg q24h
	Cefepime	2 g	1–2 g q12h	1 g q8h or 2 g q12h	Same	500–1000 mg q24h
	Cefotaxime	None	1–2 g q8–12h	1–2 g q8h	1–2 g q6–8h	1–2 g q24h
	Ceftazidime	2 g	1–2 g q12h	1 g q8 or 2 g q12	Same	500–1000 mg q24h
	Ceftriaxone	2 g	1–2 g q12–24h	Same	Same	1–2 g q24h
Monobactam	Aztreonam	2 g	1–2 g q12h	1 g q8h or 2 g q12h	Same	500 mg q12h
Penicillins +/– beta-lactamases	Penicillin G	4 MU	2 MU q4–6h	2–3 MU q4–6h	2–4 MU q4–6h	50%–100% normal dose q12–24h
	Ampicillin	2 g	1–2 g q8–12h	1–2 g q8h	1–2 g q6–8h	1–2 g q12–24h
	Ampicillin-sulbactam	3 g	1–2 g q8–12h	1–2 g q8h	1–2 g q6–8h	1.5–3 g q12–24h
	Nafcillin	None	2 g q4–6h	Same	Same	Same
	Piperacillin-tazobactam	None	2.25–3.375 g q6–8h	2.25–3.375 g q6h	3.375 g q6h	2.25 g q12h
	Ticarcillin-clavulanate	3.1 g	2 g q6–8h	3.1 g q6–8h	3.1 g q6h	2 g q12h
Quinolone	Levofloxacin	500–750 mg	250 mg q24h	250–500 mg q24h	250–750 mg q24h	250–500 mg q48h
	Ciprofloxacin	None	200–400 mg q12–24h	400 mg q12–24h	Same	200–400 mg q12–24h
	Moxifloxacin	None	400 mg q24h	Same	Same	Same
Other	TMP-SMX	None	2.5–7.5 mg/kg q12h	Same	Same	2.5–10 mg/kg q24h or 5–20 mg/kg 3x/wk after HD
	Vancomycin	15–25 mg/kg	10–15 mg/kg q24–48h	10–15 mg/kg q24h	7.5–10 mg/kg q12h	5–10 mg/kg after HD

*Based on Heintz BH, Matzke GR, Dager WE: Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. Pharmacotherapy 29:562-577, 2009.

CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; HD, hemodialysis; PO, by mouth; q4–6h, every 4 to 6 hours; q6h, every 6 hours; q8–12h, every 8 to 12 hours; q8h, every 8 hours; q12h, every 12 hours; q12–24h, every 12 to 24 hours; q24h, every 24 hours; q48–72h, every 48 to 72 hours; TMP-SMX, trimethoprim-sulfamethoxazole.

Clinical Pearls and Pitfalls

1. *Residual renal function* enhances long-term survival in ESRD. If a patient has significant urine output (greater than 250 mL daily), make an effort to preserve this residual function. Avoid radiocontrast administration, aminoglycosides, and other nephrotoxins if feasible.
2. Preserve potential vascular access sites in patients with ESRD. Avoid blood draws and intravenous catheters in the arm with existing or intended vascular access. Ideally, restrict all blood draws and catheters to the dorsum of the hand, but in practice it is virtually impossible to do so during critical illness. Peripherally inserted central catheters (PICC) typically cause venous stenosis and make arteriovenous dialysis access untenable; small bore-central venous catheters for intravenous infusions are preferred in patients with serum creatinine over 3 mg/dL. The preferred site for central venous access is the internal jugular vein (contralateral to upper extremity vascular access if present), as indwelling subclavian catheters cause subclavian stenosis and compromise venous return from existing or future arteriovenous access. A central venous dialysis catheter should not be used for other infusions or manipulated by personnel other than the dialysis staff in order to minimize risk of infection or inadvertent infusion of heparin.
3. Probably the *most common error* in the care of ESRD patients is failure to dose medications appropriately for renal failure (see Chapter 17). For examples: (1) magnesium- and phosphate-containing laxatives are contraindicated; (2) meperidine is contraindicated, whereas hydromorphone and fentanyl are the preferred opioid analgesics; and (3) phenytoin dosing is unchanged, but monitoring the free level (not the total) of the drug is advisable.
4. Care of the critically ill renal transplant recipient is complex. Immunosuppression must be continued, even if patients are taking nothing by mouth, though the cumulative dose is usually decreased by holding the antiproliferative agent (azathioprine, mycophenolate). Consult a transplant nephrologist to assist with decisions regarding immunosuppression and other organ-specific concerns.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 27

Care of the Patient with End-Stage Liver Disease

Karen L. Krok

End-stage liver disease (ESLD) encompasses the clinical manifestations generally associated with advanced cirrhosis. The term *ESLD* is used irrespective of the cause of the cirrhosis. ESLD complications include ascites, hepatic hydrothorax, spontaneous bacterial peritonitis, variceal hemorrhage, hepatic encephalopathy, and hepatorenal syndrome. These conditions may precipitate admission to the intensive care unit (ICU) or complicate the stay of ICU patients who were admitted because of another condition. Prompt identification and effective ICU management of these complications can decrease morbidity and mortality as well as serve as temporizing measures for patients awaiting liver transplantation.

All patients with ESLD should be considered for a liver transplant. Currently, the Model for End Stage Liver Disease (or MELD) score is used to prioritize patients for a deceased donor liver transplant. A prospectively developed and validated chronic liver disease severity scoring system, the MELD score uses a patient's laboratory values for serum bilirubin, serum creatinine, and the international normalized ratio (INR) for prothrombin time to predict survival. In patients with chronic liver disease, an increasing MELD score is associated with increasing severity of hepatic dysfunction and risk of death. The MELD score is calculated according to the following formula:

$$\text{MELD} = 3.8[\text{Ln serum bilirubin (mg/dL)}] + 11.2[\text{Ln INR}] + 9.6[\text{Ln serum creatinine (mg/dL)}] + 6.4$$

where Ln is the natural logarithm. Several online calculators are readily available for calculating the MELD score (e.g., optn.transplant.hrsa.gov/resources/MeldPeldCalculator.asp?index=98, accessed on June 22, 2012).

Ascites

Ascites is easily diagnosed when the abdomen is distended with a large amount of fluid by assessing for shifting dullness or flank dullness; patients need at least 1500 mL of peritoneal fluid to be detected reliably by physical examination. In less obvious cases, abdominal ultrasonography can detect as little as 100 mL of free intraperitoneal fluid and should be used in patients in whom the physical examination is unreliable.

Perform abdominal paracentesis in all ICU patients with new-onset ascites or a change in clinical status (i.e., worsening encephalopathy, increasing creatinine, increasing white blood cell count or hypo- or hyperthermia). Send ascitic fluid for cell count with differential, albumin, total protein, and bacterial culture. Prophylactic transfusions of fresh frozen plasma or platelets before paracentesis are not data supported. In fact, bleeding complications occur in fewer than 1 in 1000 paracenteses. In a study of 1100 large-volume paracenteses, there were no bleeding complications despite (1) no prophylactic transfusions, (2) platelet counts as low as 19,000 platelets/mm^3

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(54% < 50,000 platelets/mm^3), and (3) INRs as high as 8.7 (75% > 1.5 and 26.5% > 2.0). Coagulopathy should preclude paracentesis only when there is disseminated intravascular coagulation or clinically evident hyperfibrinolysis (three-dimensional ecchymoses/hematoma).

Ascites is best characterized by calculating the serum-ascites albumin gradient (SAAG) from samples obtained on the same day. A SAAG > 1.1 g/dL establishes the presence of portal hypertension and abolishes the need to check an albumin with each subsequent paracentesis.

Multiple factors may precipitate ascites (Box 27.1). Medical management (including diuretics and sodium restriction) is effective in more than 90% of patients. In the ICU, avoid excessive sodium administration in intravenous fluids. For example, the volume of normal saline intended to keep an intravenous catheter open (10 mL/h for 24 hours) contains 850 mg of sodium (because 1000 mL of 0.9% NaCl contains 154 mmol of sodium and 154 mmol of chloride, or 3542 mg of sodium since 1 mmol of sodium = 23 mg). Thus, 240 mL of 0.9% NaCl contains 850 mg of sodium (because 3542 mg of sodium/1000 mL × 240 mL = 850 mg), nearly half of the 2000 mg daily sodium restriction applied to patients with ESLD.

Spironolactone is the predominant diuretic used in ESLD. Because of a prolonged half-life of the drug and its metabolites, spironolactone may be administered once a day (generally initiated at a dose of 50 mg once per day). Furosemide at a dose of 20 mg once per day may be added to increase diuresis. While monitoring serum electrolytes and renal function, diuretics may be adjusted at 3- to 4-day intervals to a maximum of spironolactone 400 mg/day and furosemide 160 mg/day. If painful gynecomastia or other side effects occur from spironolactone therapy, amiloride, starting at 5 mg/day to a maximum of 40 mg/day, may be substituted. The goal of treatment should be weight loss of 0.3 to 0.5 kg/day in patients without peripheral edema and 0.8 to 1.0 kg/day in patients with peripheral edema. In patients on diuretics who do not achieve the desired weight loss, determine a urinary sodium; patients with urine sodium > 90 mEq/day (i.e., urine sodium greater than theoretic—and prescribed—sodium intake) are not compliant with sodium restriction. A low-sodium diet is extremely challenging to maintain and may require a nutritional consult to be successful. Unless a patient is having respiratory compromise, do not give diuretics intravenously to patients with ESLD, as this may cause a rapid fluid shift and precipitate hepatorenal syndrome.

BOX 27.1 ■ Ascites: Causes, Treatment, and Pitfalls

Precipitating Causes

Hepatocellular carcinoma, metastatic carcinoma
Noncompliance with diuretic therapy
Noncompliance with sodium restriction
Portal vein or hepatic vein thrombosis

Treatment

Sodium restriction—less than 2000 mg/day of sodium
Diuretic therapy
Large-volume paracentesis
Transjugular intrahepatic portosystemic shunt
Fluid restriction for low serum sodium (< 130 mEq/L)
Transplantation

Pitfalls

Intravascular volume depletion
Metabolic derangements (hyponatremia, hypokalemia)
Hepatorenal syndrome (HRS)
Spontaneous bacterial peritonitis (SBP)
Hepatohydrothorax

Refractory ascites cannot be mobilized or recurs early despite sodium restriction and diuretic treatment. Alternatively, refractory ascites may reflect the development of diuretic-induced complications that preclude the use of an effective diuretic dose. Refractory ascites occurs in only 10% of patients with ascites. Treatment strategies include repeated therapeutic paracentesis plus intravenous albumin or the use of a transjugular intrahepatic portosystemic shunt (TIPS). Large-volume paracentesis (4 to 8 L) may provide symptomatic relief in patients with ascites. If greater than 4 liters of fluid are removed, albumin should be administered intravenously at a dose of 8 g of albumin per liter of fluid removed—that is, if 5 L of fluid are removed, then 40 g of albumin should be given (5 L × 8 g/L removed = 40 g).

A TIPS is a nonsurgical method of portal decompression that consists of inserting an intrahepatic stent between one hepatic vein and the portal vein using a transjugular approach. Reduction in portal pressure is accompanied by a resolution of ascites in most patients. TIPS may be associated with several side effects and complications and is usually contraindicated in elderly patients aged > 70 to 75 years. These include hepatic encephalopathy, obstruction of shunt, congestive heart failure, hemolytic anemia, and impairment in liver function.

Hepatic Hydrothorax

Hepatic hydrothorax is a large pleural effusion (> 500 mL) in a patient with cirrhosis and no coexisting cardiopulmonary diseases. The prevalence in cirrhotic patients is 5% to 10%, and 85% of cases are right-sided. The most likely etiology is the free passage of ascites from the peritoneal cavity through defects located in the tendinous portion of the diaphragm. When hepatic hydrothorax is suspected, perform a diagnostic thoracentesis and send the fluid for cell count, Gram stain and culture, protein, lactate dehydrogenase (LDH), albumin, and bilirubin. In uncomplicated hepatic hydrothorax, the cell count is < 500 cells/mm^3 and the total protein < 2.5 g/dL.

All patients should be started on a low-sodium diet and diuretics, as described for the treatment of ascites. A refractory hepatic hydrothorax persists despite fluid and sodium restriction and use of maximal tolerated doses of diuretics and warrants evaluation for TIPS placement. In general, avoid insertion of a long-term pleural catheter or chest tube as a potential nidus for infections and excessive fluid losses.

Spontaneous Bacterial Peritonitis (SBP)

Gram-negative bacteria, particularly *Escherichia coli*, are responsible for 80% of cases of SBP. *Streptococcus viridans*, *Staphylococcus aureus,* or *Enterococcus fecalis* will be isolated in the remaining 20% of cases. The diagnosis of SBP is made when the ascitic fluid has > 250/mm^3 neutrophils. A positive culture is not needed for the diagnosis of SBP. A "clinical" diagnosis of infected ascitic fluid without a paracentesis is *not* adequate.

An intravenous third-generation cephalosporin (cefotaxime or ceftriaxone) for 5 to 7 days is the treatment of choice for SBP. Renal insufficiency may occur in up to one third of patients with SBP, related to impaired circulatory function with activation of the vasoconstrictor systems. Attempting to prevent this complication, administer albumin intravenously at a dose of 1.5 g/kg at the diagnosis of the infection and 1.0 g/kg 48 hours later.

Patients with SBP have a very poor 1-year survival of only 30% to 50%. Therefore, evaluate all patients for liver transplantation after recovery from their first episode of SBP. Treat patients indefinitely with oral SBP prophylaxis, with norfloxacin 400 mg daily, ciprofloxacin 250 mg daily, or double-strength trimethoprim-sulfamethoxazole at least five times a week.

Two conditions associated with an increased risk of SBP warrant primary prophylaxis of SBP. First, in patients with gastrointestinal hemorrhage, multiple studies have shown that a short-term (7-day) administration of oral norfloxacin 400 mg twice a day or intravenous ceftriaxone

1 gm/day reduces the incidence of SBP, bacteremia, and rebleeding. Second, patients with a serum creatinine > 1.2 mg/dL, ascitic fluid protein levels < 15 g/L, a Child-Pugh score > 9, or dilutional hyponatremia (serum sodium < 130 mEq/L) should receive prophylaxis. In a randomized, placebo-controlled trial, primary prophylaxis with oral norfloxacin (400 mg/day) reduced the 1-year probability of developing SBP (7% versus 61%) and hepatorenal syndrome (28% versus 41%) and improved the 3-month survival (94% versus 62%) and the 1-year survival (60% versus 48%) compared with placebo.

Variceal Hemorrhage

Gastroesophageal varices are present in approximately 50% of patients with cirrhosis. Among the complication of ESLD, varices correlate most directly with portal hypertension. Patients with cirrhosis and gastroesophageal varices have a hepatic venous pressure gradient (wedged hepatic pressure minus free hepatic pressure) of at least 10 to 12 mm Hg (normal is 3 to 5 mm Hg). Variceal hemorrhage occurs at a yearly rate of 5% to 15%, and the most important predictor of hemorrhage is the size of the varices. Other predictors of hemorrhage are decompensated cirrhosis and the endoscopic presence of red wale marks (raised, longitudinal red streaks).

Active upper gastrointestinal (GI) bleeding in a patient with ESLD requires admission to the ICU and prompt evaluation and treatment (see Chapter 61). The management of variceal bleeding differs markedly from other causes of upper GI hemorrhage, with early endoscopy critical for identifying the source of bleeding and directing appropriate treatment.

Approximately one third of patients with varices bleed from them within 2 to 5 years. Patients who have never bled from esophageal varices are candidates for nonselective beta-blockade prophylaxis with propranolol or nadolol, administered with the goal of decreasing the resting heart rate 25% to a minimum of 60 beats per minute.

The mortality rate from variceal bleeding is at least 20% at 6 weeks. The risk of recurrent variceal bleeding is increased during the first 6 weeks after the initial bleeding episode, particularly during the first several days. The goals of ICU management are to stop variceal bleeding, prevent recurrent bleeding, and avoid complications, which can include decompensated liver function, aspiration pneumonia, acute renal failure, SBP, and encephalopathy.

Patients with ESLD who are actively bleeding should be resuscitated cautiously with intravenous fluids and blood products. Transfuse packed red blood cells with the goal to maintain hemodynamic stability and hemoglobin of approximately 8.0 g/dL. This recommendation is based on experimental studies showing that replacement of all lost blood leads to an increase in portal pressure with more rebleeding and mortality. Fresh frozen plasma and platelets are transfused when the patient has a coagulopathy, usually as a result of impaired hepatic synthetic function and splenic sequestration of platelets. Recombinant factor VIIa in cirrhotic patients with gastrointestinal hemorrhage is not recommended, as it is unproven to be beneficial over standard therapy. Given that aspiration of blood can occur, elective or more emergent tracheal intubation may be required for airway protection prior to endoscopy, particularly in patients with hepatic encephalopathy.

Patients with ESLD and variceal bleeding have a high risk of developing severe bacterial infections (SBP and other infections) associated with early recurrence of variceal hemorrhage and a greater mortality. The use of short-term prophylactic antibiotics in patients with ESLD regardless of the presence of ascites decreases the rates of bacterial infections, rebleeding, and mortality. Norfloxacin 400 mg orally twice a day for 7 days, intravenous quinolones, and intravenous ceftriaxone (1 g/day) are the recommended treatment regimens.

Endoscopic therapy sclerosis or band ligation is effective at stopping bleeding esophageal varices in more than 80% of cases. Pharmacologic therapy for bleeding esophageal varices is achieved with intravenous octreotide, administered as a 50-μg intravenous bolus followed by a 50-μg/h continuous infusion for 72 hours. Do not use beta-blockers in the acute setting as they will

decrease blood pressure and blunt the tachycardia associated with bleeding. Once the acute event is controlled and the patient is stabilized, initiate nonselective beta-blockers.

A Minnesota or Sengstaken-Blakemore tube (a tamponading tube) may be inserted as a temporizing measure when endoscopic and pharmacologic therapies have failed. However, its use is associated with many complications including aspiration, migration, and necrosis/perforation of the esophagus. Airway protection with tracheal intubation is strongly recommended when using a balloon tamponade. Also, note that the gastric balloon is the only balloon that should be inflated. A TIPS can be lifesaving in patients with variceal bleeding refractory to endoscopic and pharmacologic therapy. Hemorrhage from gastric varices is also an indication for TIPS placement, as endoscopic management has limited efficacy. Complications of TIPS have been discussed earlier in the section on ascites.

Ablating the esophageal varices with repeated banding treatments decreases the risk of long-term rebleeding. After a variceal bleed, patients should be discharged from the hospital on a nonselective beta-blocker (if tolerated), with a repeat endoscopy scheduled for 3 to 4 weeks from the initial endoscopy.

Hepatic Encephalopathy

Hepatic encephalopathy is a disturbance of cerebral function in the setting of liver disease. Hepatic encephalopathy appears to be due to reduced hepatic clearance of toxins that impair brain function. Altered cerebral function ranges from mild disturbances in thought or affect to deep coma, generally graded on a four-stage clinical scale (Table 27.1).

Hepatic encephalopathy is a challenging complication of advanced liver disease. Overt forms occur in 30% to 45% of patients with liver cirrhosis and in 10% to 50% of patients with TIPS. Minimal hepatic encephalopathy, characterized by more subtle motor and cognitive deficits, affects approximately 20% to 60% of patients with liver disease. The development of hepatic encephalopathy is an ominous sign, carrying a 58% 1-year mortality and a 67% 3-year mortality.

Hepatic encephalopathy is diagnosed on clinical grounds. Serum ammonia levels are often elevated in patients with hepatic encephalopathy but correlate poorly with the degree of hepatic encephalopathy. An elevated ammonia level in a coherent patient does not warrant treatment with lactulose. Asterixis may disappear as hepatic encephalopathy progresses to grades III and IV. It is important to exclude other causes for a change in mental status, such as hypoglycemia, head trauma, meningitis, encephalitis, drug toxicity, toxins (such as alcohol), and seizures with a postictal state.

TABLE 27.1 ■ **Grading Scale for Hepatic Encephalopathy**

Grade	Symptoms	Signs	Electroencephalographic Findings
I	Subtle change in mental status, difficulty in computation, emotional lability	No asterixis	Normal or symmetric slowing, triphasic waves
II	Drowsy, unequivocal loss of computation, memory loss	Asterixis	Abnormal symmetric slowing, triphasic waves
III	Sleepy but arousable, can answer simple questions only	Asterixis (if able to comply)	Abnormal symmetric slowing, triphasic waves
IVa	Coma, no response to commands, responds to pain	Unable to comply for asterixis testing, Babinski reflex is present	Abnormal slow delta waves (2–3/min)
IVb	Coma, no response to commands or pain	Same as in IVa	Same as in IVa

BOX 27.2 ■ Hepatic Encephalopathy in Patients with End-Stage Liver Disease: Causes, Treatment, and Pitfalls

Precipitating Causes

Increased nitrogen load: Gastrointestinal bleeding, excess dietary protein, azotemia, constipation
Toxins (acetaminophen, ethanol)
Electrolyte imbalance: Hyponatremia, hypokalemia, metabolic alkalosis/acidosis, hypoxia, hypovolemia
Miscellaneous: Infection (pneumonia, urinary tract infection, cellulites, spontaneous bacterial peritonitis [SBP], etc.), surgery, superimposed acute liver disease, progressive liver disease, transjugular intrahepatic portosystemic shunt (TIPS)
Noncompliance with medical therapy
Medications: Benzodiazepines, opioids, other sedatives or tranquilizers

Treatment

Lactulose orally (or, if not possible, by enemas)
Treat infection
Nonabsorbable antibiotics (neomycin, metronidazole, rifaximin) orally (in addition to lactulose in refractory cases)

Pitfalls

Do not diagnose hepatic encephalopathy based solely on the presence of elevated serum ammonia levels
Exclude other causes for a change in mental status (hypoglycemia, head trauma, meningitis, encephalitis, drug toxicity, toxins, and seizures)
There is no need to protein restrict these patients—in fact, protein restriction may lead to worsening of their cachexia

An important goal of therapy for hepatic encephalopathy is the identification and correction of precipitating causes that may occur alone or in combination (Box 27.2). Encephalopathy may be the first clinically apparent sign of GI bleeding or sepsis. If ascites is present, a paracentesis is *essential* to exclude SBP. All patients should have blood cultures, urinalysis, and a chest radiograph performed.

Initial treatment with oral lactulose is at high doses (30 mL every 1 to 2 hours) until a stool is passed. After the first stool, lactulose dosage is decreased to 30 mL every 6 to 8 hours and titrated to achieve a maximum of three to four soft, formed bowel movements per day. If lactulose cannot be administered orally, it may be administered as an enema at a dose of 300 mL lactulose + 700 mL tap water or saline every 4 to 6 hours as needed.

Most patients can be managed with titrated lactulose therapy and modest protein restriction (1 g/kg of protein per day). If necessary, additional antibiotic treatment can reduce the mass of enteric bacteria that produce ammonia. Metronidazole at 250 mg three times a day orally has been reported in small case series to show some benefit, although patients should be warned of the potential neurotoxicity seen with long-term use of metronidazole at higher doses. Rifaximin at a dose of 400 mg three times a day or 550 mg twice a day has been studied in the treatment of hepatic encephalopathy, after receiving "orphan status" by the Food and Drug Administration for this indication.

Chronic hepatic encephalopathy is almost always reversible. If it does not resolve within 72 hours of treatment, an ongoing precipitating factor, another cause of encephalopathy, or suboptimal treatment should be considered.

Hepatorenal Syndrome (HRS)

Renal insufficiency in patients with ESLD is a common problem in the ICU. Avoid conditions and medications that may precipitate renal insufficiency, such as hypovolemia, nonsteroidal anti-inflammatory drugs, and aminoglycosides. When renal insufficiency develops in the ICU patient with ESLD, the most common conditions are acute tubular necrosis, prerenal azotemia, and

hepatorenal syndrome (HRS). Analysis of urine electrolytes (urine Na > 10 mEq/L) and examination of the urine sediment (presence of casts) can usually differentiate acute tubular necrosis from the other two conditions. The characteristics of the urine from patients with HRS are indistinguishable from those with hypovolemia. Differentiation between these two conditions depends on an assessment of intravascular status, which is difficult in patients with ESLD. In most cases, one gives a fluid challenge with albumin (ideally) or normal saline and observes the response. In some cases, a pulmonary artery catheter may be needed to answer the question definitively.

As there are no specific hallmarks for HRS, the diagnosis is based on excluding other forms of renal disease. The diagnostic criteria for HRS as determined by the International Ascites Club include (1) cirrhosis with ascites; (2) serum creatinine > 1.5 mg/dL; (3) no improvement of serum creatinine (i.e., failure to decrease to a level of < 1.5 mg/dL) after at least 2 days with diuretic withdrawal and volume expansion with albumin (the recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day); (4) absence of shock; (5) no current or recent treatment with nephrotoxic drugs; and (6) absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/day, microhematuria (> 50 red blood cells per high power field), or abnormal renal ultrasonography. Although HRS has a poor prognosis, it is generally reversible with liver transplantation. Diuretics should be discontinued and dialysis considered as a temporizing measure for patients awaiting liver transplantation.

HRS is divided into two types, depending on the rate of decline in a patient's glomerular filtration rate. In type 1 HRS, kidney function declines very rapidly in less than 2 weeks, whereas in type 2, this decline occurs over months. The prognosis is very different for these two forms of HRS. In type 1 HRS, the median survival is 1 month, whereas type 2 HRS patients with MELD scores > 20 have a median survival of 3 months and those with a MELD < 20 have a median survival of 11 months. The main pathogenic mechanism in type 1 HRS is a potentially reversible deterioration of systemic circulatory function, mostly because of splanchnic vasodilatation and renal vasoconstriction and often triggered by a precipitating event. In addition to renal failure, the syndrome may be associated with other organ dysfunctions, such as decreased cardiac output, hepatic failure, and encephalopathy.

The treatment of HRS is designed to expand the central blood volume by simultaneously increasing the total plasma volume and reducing the intense peripheral vasodilatation. Patients ideally should be administered a vasopressin analogue, such as terlipressin, plus albumin; terlipressin has not yet been approved for use in the United States but has had widespread use in Europe. The mechanism by which vasoconstrictors and albumin improve the glomerular filtration rate in patients with HRS is not completely understood. It is hypothesized that vasopressin analogues cause vasoconstriction of the splanchnic bed, thereby allowing redistribution of the blood volume to extrasplanchnic organs including the kidneys. Filling of the central vascular compartment inhibits the sympathetic nervous and renin–angiotensin systems, thereby making renal blood flow and glomerular filtration rate more responsive to changes in blood pressure. Albumin is traditionally considered to improve circulatory function in cirrhosis by expanding central blood volume and increasing cardiac output. It is therefore conceivable that an improvement of renal function in patients with HRS treated with vasoconstrictors and albumin is due to the additive effects that the two compounds have on cardiac function and peripheral arterial circulation.

In the United States, midodrine (a selective alpha-1 adrenergic agonist) and octreotide (a somatostatin analogue) with albumin are used for the treatment of HRS. The dosages are as follows: octreotide is 100 to 200 μg three times a day subcutaneously, midodrine starting at 5 mg three times a day orally and increased to a maximum of 15 mg three times a day or a goal of an increase in the mean arterial pressure of 15 mm Hg, and IV albumin 50 g daily. Liver transplantation, however, is the only treatment that ensures long-term survival.



An annotated bibliography can be found at www.expertconsult.com.

Conclusion

Patients in the ICU with ESLD require an attention to detail and diligent care. Prompt identification and effective management of problems related to their ESLD, including variceal hemorrhage, ascites, SBP, encephalopathy, and HRS, can decrease their associated morbidity and mortality and allow patients to get the lifesaving liver transplant required for long-term survival.

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CHAPTER 28

Care of the Maternal-Fetal Unit

Christopher Nold ■ Samuel Parry

Care of the obstetric patient in the intensive care unit (ICU) presents a number of challenges. For example, maternal physiologic changes in pregnancy and concerns for the fetus often make the diagnosis of conditions commonly seen in critical illness more difficult and their treatment more complicated than in nonpregnant ICU patients. This chapter discusses maternal changes in pregnancy relevant to the ICU, how standard ICU interventions should be modified when treating pregnant patients, and when fetal monitoring should be used.

Maternal Physiologic Changes in Pregnancy

HEMATOLOGIC CHANGES

Maternal plasma volume increases ~50% above baseline by 30 to 34 weeks of pregnancy. *Red blood cell mass* also increases throughout gestation, but to only 18% to 30% more than nonpregnancy levels. These two phenomena result in a physiologic anemia, with the nadir of hemoglobin concentration (usually between 11 and 12 g/dL) at approximately 30 weeks of gestation. *White blood cell counts* during pregnancy also may increase (secondary to increased numbers of circulating granulocytes), with the upper limits of a pregnant woman's normal white blood cell count being in the 15,000 to 16,000/μL range. *Platelet counts* remain greater than 150,000/μL during gestation, despite increased platelet turnover and a slightly shortened platelet life span.

Pregnancy has been described as a *hypercoagulable state* for the most part because of estrogen-induced increases in hepatic production of clotting factors I (fibrinogen), VII, IX, and X. Although pregnant patients have normal bleeding and clotting times, they are at increased risk for venous thromboembolism. This is particularly true in the puerperium (i.e., childbirth to 3 to 6 weeks postpartum) when injury to large pelvic veins or venous stasis in lower extremity veins is likely to occur. Any pregnant patient in whom there is prolonged restriction to activity should be considered a candidate for prophylaxis of deep venous thrombosis and should be fitted with pneumatic compression stockings or receive prophylactic anticoagulation (enoxaparin 40 mg subcutaneous daily, dalteparin 5000 IU mg subcutaneous daily, or heparin 5000 to 10,000 units subcutaneous twice per day).

HEMODYNAMIC CHANGES

Blood pressure normally decreases during pregnancy secondary to decreased peripheral vascular resistance, an effect of circulating progesterone. The lowest values are seen at 24 to 28 weeks of gestation. Mean systolic blood pressure measures 5 to 10 mm Hg below baseline, whereas diastolic blood pressure falls slightly more, 10 to 15 mm Hg. Mean maternal heart rate increases at the beginning of the third trimester. Cardiac output is increased by 10 weeks of gestation secondary to increased stroke volume and later, in the third trimester, because of an increased heart rate (+15%). In large part, other changes in hemodynamic parameters result from the increased plasma volume associated with pregnancy (Table 28.1).

TABLE 28.1 ■ **Hemodynamic Changes Associated with Late Pregnancy**

	Nonpregnant*	Pregnant*
Cardiac output (L/min)	4.3 (±0.9)	6.2 (±1.0)
Systemic vascular resistance (dyne x s/cm^5)	1530 (±520)	1210 (±266)
Colloid oncotic pressure (COP) (mm Hg)	20.8 (±1.0)	18 (±1.5)
Pulmonary artery wedge pressure (PAWP) (mm Hg)	6 (±2)	8 (±2)
COP-PAWP gradient (mm Hg)	14.5 (±2.5)	10.5 (±2.7)

*Means (± standard errors).
From Clark SL, Cotton DB, Lee W, et al: Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol 161:1439-1442, 1989.

When a pregnant patient lies supine, the gravid uterus compresses the inferior vena cava leading to decreased venous return and cardiac output. Normally, peripheral vascular resistance increases to compensate for the decreased venous return. However, in up to 10% of pregnant patients, this protective mechanism fails. These patients have *supine hypotension of pregnancy* and become lightheaded or syncopal when supine. Maternal hemodynamics are optimized when the patient is placed in a left lateral recumbent position. Because blood pressure during pregnancy can vary with postural changes, serial blood pressure measurements should be obtained consistently with the pregnant patient in one position, with the cuff and heart at the same height from the floor.

PHYSICAL FINDINGS ATTRIBUTABLE TO PREGNANCY

Pregnant patients often have dependent edema secondary to decreased colloid oncotic pressure, increased lower extremity venous pressure, and obstruction of lymphatic flow by the gravid uterus. The first heart sound is often split, and a third heart sound can be auscultated in most pregnant patients secondary to increased plasma volume. Although almost all pregnant patients have a systolic ejection murmur secondary to increased flow across the aortic and pulmonic valves, diastolic murmurs are not considered physiologic during pregnancy. Electrocardiography often demonstrates a 15-degree left axis deviation because of elevation of the heart by the gravid uterus. Echocardiography may demonstrate functional tricuspid regurgitation secondary to a dilated tricuspid valve annulus. Chest radiographs will typically reveal an enlarged cardiac silhouette secondary to hypervolemia.

POSTPARTUM HEMODYNAMIC FLUCTUATIONS

Maternal blood loss from vaginal delivery of a singleton gestation averages ~500 mL. It can be two times that for a cesarean delivery. In the postpartum period, the mother mobilizes extracellular fluid, resulting in a postpartum diuresis equivalent to approximately 3 kg of weight loss. Despite the blood loss and diuresis, stroke volume and cardiac output remain elevated because of increased venous return. The clinical significance of these changes is manifested in a subclass of preeclamptic patients (see Chapter 72) as follows: (1) before delivery they have generalized vasospasm and intravascular volume depletion, (2) postpartum they mobilize their extracellular fluid as expected, (3) they often fail to diurese secondary to restricted renal blood flow, and (4) this places them at high risk for pulmonary or cerebral edema.

RESPIRATORY CHANGES

Alterations in maternal lung volumes, respiratory mechanics, and arterial blood gas values precede elevation of the diaphragm because of the gravid uterus. Respiratory rate does not change

during pregnancy, but tidal volume expands by 30% to 40%. This results in an increased minute ventilation beginning in the first trimester. Progesterone acting on the central respiratory center modulates these changes. Although gravid women frequently report a mild pregnancy-associated dyspnea, their forced expiratory volume in 1 second (FEV_1) is not decreased. Arterial pH remains at 7.40 during pregnancy, whereas Pao_2 is normally elevated at 104 to 108 mm Hg (as a result of chronic hypocapnia via the alveolar gas equation [Equation 12 in Box 1.1 in Chapter 1]), and $Paco_2$ is normally decreased at 27 to 32 mm Hg (secondary to the increased minute ventilation and increased alveolar ventilation [Box 1.1 in Chapter 1]). Increased renal excretion of bicarbonate (normal serum levels in pregnancy are 18 to 21 mEq/L) compensates for decreased $Paco_2$ and maintains the neutral pH. The lower maternal $Paco_2$ facilitates fetal-maternal CO_2 diffusion.

RENAL CHANGES

Expanded plasma volume and decreased systemic vascular resistance result in increased renal plasma flow (+75%) and glomerular filtration rate (+30% to 50%) during pregnancy. A normal creatinine clearance during pregnancy is 150 to 200 mL/minute, and serum creatinine values decrease to 0.5 to 0.6 mg/dL. Glycosuria is *not* abnormal during pregnancy secondary to increased filtration of glucose. It is important to consider the increased renal clearance of drugs when dosing patients during pregnancy. Although strict guidelines cannot be provided, obtaining drug levels when applicable is recommended.

GASTROINTESTINAL CHANGES

The smooth muscle relaxing effects of progesterone result in delayed gastric emptying, gastroesophageal sphincter relaxation, and esophageal reflux. These predispose pregnant patients to aspiration during emergency endotracheal intubation. Portal venous compression during pregnancy increases the likelihood of portal hypertension in patients with underlying chronic liver disease. Clinical presentations of this condition range from hemorrhoids to esophageal varices.

Effects of Common Intensive Care Unit Interventions on the Maternal-Fetal Unit

DRUG THERAPY

Most drugs used in critical care have not been studied extensively in the pregnant population so that little is known regarding their adverse effects on the human fetus. Although the potential risks on the fetus must be considered, as a general rule, the need to treat critical illness to restore maternal well-being should far outweigh these considerations. All drugs are assigned to categories representing degrees of fetal risk (Table 28.2). These categories are indicated in parentheses for the drugs discussed in the following sections.

Dopamine (Category C) and Dobutamine (Category B)

Dopamine has been used in renal doses to augment urine output in oliguric patients with preeclampsia without adverse fetal effects. Dobutamine has not been studied in human pregnancy. A concern for both agents is whether they decrease uterine blood flow. Animal studies of dopamine have not shown any consistent effect.

Epinephrine (Category C)

Because epinephrine is a naturally occurring agent, its effects on the fetus are difficult to discern in comparison with the effects of endogenous epinephrine and a maternal disease state. In

TABLE 28.2 ■ **Categories of Fetal Risk Factors Assigned to All Medications**

Category A	Controlled studies in humans fail to show a risk to the fetus in the first trimester
Category B	Animal studies have not demonstrated a fetal risk, but controlled studies have not been performed in humans, *or* animal studies have shown adverse effects but those have not been confirmed in controlled human studies
Category C	Animal studies have shown adverse effects and no controlled human studies have been performed, *or* studies in animals and humans have not been performed
Category D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk
Category X	The drug is contraindicated based on its demonstrated capacity to cause fetal abnormalities

asthmatics, use of subcutaneous or endotracheal epinephrine appears to be safe. When a pressor agent is required for maternal hypotension—for example, after conduction anesthesia—*ephedrine* (category C) appears to be the drug of choice because it does not decrease uterine blood flow.

Antihypertensive Agents

Since swings in maternal blood pressure may cause decreased uterine blood flow and fetal compromise, pregnant patients who are being treated with intravenous antihypertensive medications require continuous fetal monitoring. In general, obstetricians attempt to maintain systemic blood pressure at approximately 140/90 mm Hg in hypertensive patients.

Hydralazine (category C) is one of two standard intravenous antihypertensive agents used in obstetrics, but its direct relaxation of arteriolar smooth muscle has been associated with maternal hypotension, decreased uterine blood flow, and transient fetal distress. Recommended dosing of hydralazine is 5 to 10 mg intravenously, which may be repeated every 20 minutes until hypertension has been controlled. The total titrated dose should then be given every 6 hours.

Labetalol (category C) is the second standard intravenous antihypertensive agent used in obstetrics, and labetalol is not associated with decreased uterine blood flow. Labetalol may also augment fetal pulmonary surfactant secretion and decrease the risk of developing neonatal respiratory distress syndrome. Labetalol may be given as a 10-mg intravenous bolus with increasing boluses (20 mg, 40 mg, 80 mg) repeated every 10 minutes to a total dose of 300 mg. When desired blood pressure is attained, an intravenous labetalol drip may be instituted at 1 to 2 mg/minute and titrated accordingly.

Nitroglycerin (Category C)

The Collaborative Perinatal Project has demonstrated an increased rate of congenital malformations after exposure to vasodilators in the first trimester, but the effects of any single drug, including nitroglycerin, were not examined separately. When administrated for maternal hypertension, only transient fetal heart rate abnormalities, without abnormal umbilical blood gas values or Apgar scores, have been demonstrated. Intravenous nitroglycerin has been used to correct maternal blood pressure rapidly and to treat pregnancy-induced hypertension complicated by hydrostatic pulmonary edema successfully.

Sodium Nitroprusside (Category C)

Because sodium nitroprusside has been shown to cross the placenta in animals and produce fetal cyanide levels that exceed those of the mother, one should avoid its prolonged use. Monitoring maternal serum pH and thiocyanate and methemoglobin levels has been recommended. Standard doses of nitroprusside for short periods do not pose a major risk of accumulating cyanide in the fetal liver.

Contraindicated Antihypertensive Agents

Oral *nifedipine* (category C) has been used safely in humans for the treatment of hypertension in pregnancy. Intravenous nifedipine has been shown to decrease uterine blood flow in pregnant sheep. Furthermore, when given intravenously or sublingually, it may precipitate an exaggerated hypotensive response, especially when used in conjunction with magnesium sulfate in the obstetric population.

As a class, angiotensin-converting enzyme inhibitors (e.g., enalapril and captopril, both category D) and angiotensin receptor blockers should be avoided in obstetric patients. These drugs precipitate fetal hypotension and decrease fetal renal blood flow and urine output. The resultant oligohydramnios has been associated with a variety of congenital malformations.

Diuretics

Thiazide diuretics (category B) diminish the physiologic volume expansion of pregnancy but do not alter the course of pregnancy-induced hypertension. This class of drugs is associated with decreased uterine blood flow and mild neonatal thrombocytopenia. *Furosemide* (category C) is used commonly in pregnancy to treat pulmonary edema.

Antiarrhythmic Agents

Antiarrhythmic drugs have been used in pregnancy for both maternal and fetal indications (tachyarrhythmias, congestive heart failure). *Digitalis* (category C) dosing must be carefully monitored, as the expanded maternal volume of distribution may be associated with subtherapeutic levels. No reported fetal malformations have been attributed to digitalis. By term, umbilical cord levels approach 85% of maternal serum levels, and digitalis has been the drug of choice for fetal indications. The following antiarrhythmic agents—*lidocaine* (category B), *quinidine* (category C), *procainamide* (category C), and *flecainide* (category C)—have not been associated with fetal anomalies at therapeutic doses. Lidocaine has been used extensively as an anesthetic in obstetric patients, but high fetal plasma levels have been associated with central nervous system depression and low Apgar scores. Quinine, an optical isomer of quinidine, has been associated with cranial nerve VIII damage, and its use should be avoided. Damage to the auditory nerve has not been reported with quinidine. *Adenosine* (category C) has demonstrated no teratogenicity in animals, and its short half-life (<10 seconds) precludes changes in fetal heart rate.

Sedatives, Opioids, and Neuromuscular Blocking Agents

Sedatives, opioids, and neuromuscular blocking agents do not demonstrate consistent anomalies in exposed fetuses (Table 28.3). The drugs are listed in pregnancy risk factor categories B through D, mostly because little data exist in humans or in animal models. Each of the drugs listed in Table 28.3 should be used as needed in the critically ill obstetric patient.

MODIFICATIONS OF CARDIOPULMONARY RESUSCITATION FOR PREGNANT WOMEN

No changes are recommended in closed chest compressions and dosing of pharmacologic agents. Limited information is available regarding electric shock in pregnancy, and defibrillation should be performed according to advanced cardiac life support (ACLS) algorithms (see Appendix E). Uterine displacement using a wedge or pillow will decrease aortocaval compression by the gravid uterus and enhance maternal cardiac output. Airway management may be complicated by aspiration of gastric contents before or during endotracheal intubation.

Fetal oxygenation reflects uterine venous Po_2, which is the maximal Po_2 that can be achieved by diffusion of oxygen in the placental vasculature. The increased affinity of fetal hemoglobin for oxygen shifts the fetal hemoglobin saturation curve to the left when compared with adult

TABLE 28.3 ■ **Sedatives, Opioids, and Neuromuscular Blocking Agents Used in Pregnancy**

Drug (Fetal Risk Category)	Teratogenic Effects	Comments
Sedatives		
Diazepam (D)	Cleft lip and palate (mice)	Rapid equilibration across the placenta
	Neurobehavioral delays (rats)	Accumulates at higher levels in the fetus than in the mother
		Neonatal withdrawal
Midazolam (D)	No teratogenicity in animal studies or in isolated human reports	Crosses the placenta less efficiently than does diazepam
Lorazepam (D)		Neonatal withdrawal
Opioids		
Morphine (C)	None	Rapid placental transfer
Fentanyl (C)		Neonatal respiratory depression, withdrawal
Meperidine (C)	None	Rapid placental transfer
		Less respiratory depression, withdrawal in the neonate
Neuromuscular Blocking Agents		
Cisatracurium (B)	No adverse effects in pregnant rats	
Pancuronium (C)		
Vecuronium (C)	No animal or human studies	Inefficient placental transfer
		Alert neonatologist of potential need for ventilatory support

hemoglobin (see Appendix A). This shift promotes oxygen loading from maternal hemoglobin to fetal hemoglobin but hinders oxygen unloading from fetal hemoglobin. Thus, fetal oxygen saturation begins to fall rapidly if maternal arterial Po_2 falls to less than 60 mm Hg. Interventions to improve fetal oxygenation include maternal volume expansion, correction of maternal acidosis and fever, and enhanced maternal oxygen delivery (Figures 28.1 and 28.2).

The question of whether to do a perimortem cesarean section remains controversial. Primate fetuses have demonstrated brain damage after 6 minutes of maternal asphyxia. In one large study, if the fetuses were delivered within 5 minutes of maternal cardiopulmonary arrest, 70% of neonates survived and all survivors were neurologically intact. The American College of Obstetrics and Gynecology has recommended a theoretic 4-minute limit for the performance of a perimortem cesarean section if the threshold of fetal viability (generally accepted at 24 weeks of gestation) has been reached. Importantly, cesarean delivery should not be attempted if the mother's condition is unstable.

IMAGING STUDIES IN PREGNANCY

No fetal malformations have been reported at radiation exposures less than 50 mSv ~5 rem for radiographs and gamma rays, and most investigators believe there is no serious risk to the fetus with exposures less than 100 mSv (10 rem). At less than 4 weeks' gestation, ionizing radiation has an all-or-none effect, potentially causing a spontaneous abortion. Organogenesis occurs during the 4th to 12th weeks of pregnancy, during which ionizing radiation may be associated with major fetal malformations, including microcephaly and growth retardation. The fetal central nervous

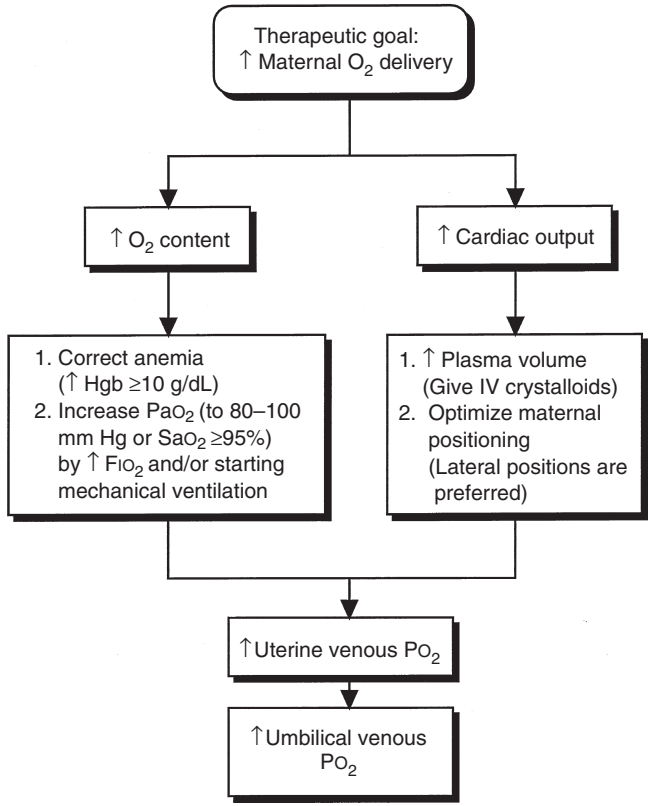


Figure 28.1 Schematic flow diagram illustrating the approach to improving fetal oxygenation by increasing maternal oxygen delivery. O_2, oxygen; Hgb, hemoglobin; Pa_{O_2}, partial pressure of arterial oxygen; Sa_{O_2}, arterial blood saturation with oxygen; F_{IO_2}, fraction of inspired oxygen; IV, intravenous; P_{O_2}, partial pressure of oxygen; ↑ indicates increase.

system continues to develop rapidly up to 16 weeks of gestation, and high doses of ionizing radiation during this time may result in mental retardation. Later in pregnancy, radiation is associated with side effects similar to those in the adult, including bone marrow suppression. There may also be a 50% increase in childhood cancers—that is, an increased rate from 1 in 3000 to 1 in 2000. Radiation doses associated with various diagnostic procedures are almost universally less than 50 mSv (5 rem) (Table 28.4). One should consult with the appropriate radiologist to calculate the dose of ionizing radiation associated with a diagnostic procedure not listed.

Iodine radioisotopes are contraindicated because they accumulate in the fetal thyroid gland. Ultrasonography is not associated with any risk of fetal malformations. Magnetic resonance imaging has not been reported to cause fetal malformations.

Fetal Monitoring

Since the 1980s, obstetricians have used fetal heart rate patterns to assess fetal well-being. Importantly, an abnormal tracing does not always predict an adverse fetal outcome. Nevertheless, in the critically ill obstetric patient, fetal heart rate patterns often reflect maternal oxygenation and the status of uterine perfusion. A nonexhaustive list of indications for continuous fetal heart rate monitoring in the ICU is given in Table 28.5.

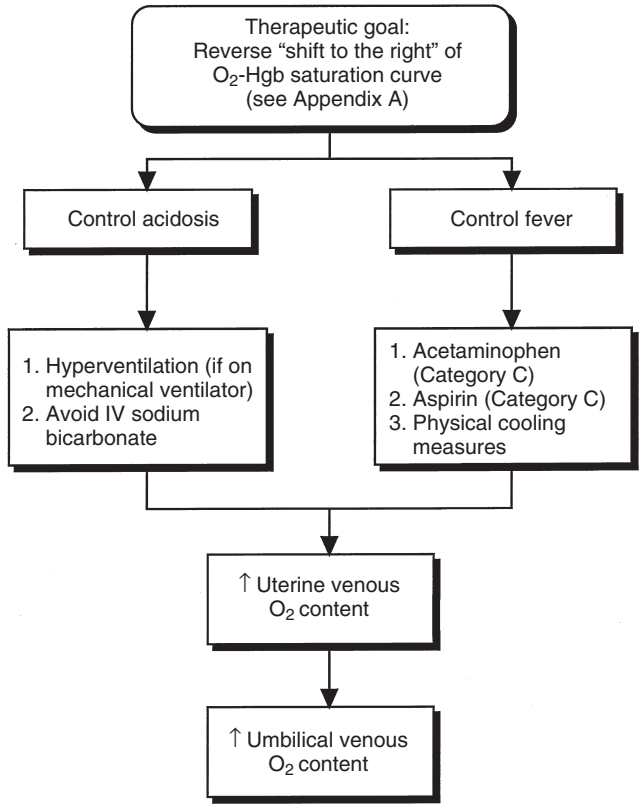


Figure 28.2 Schematic flow diagram illustrating the approach to improving fetal oxygenation by reversing the shift to the right of the oxyhemoglobin (O_2-Hgb) saturation curve induced by acidosis and fever (Appendix A). Because bicarbonate does not pass the placenta, its administration will decrease maternal hyperventilation (in a spontaneously breathing patient) and, consequently, lead to a rise in maternal and fetal $Paco_2$. O_2, oxygen; Hgb, hemoglobin; IV, intravenous.

TABLE 28.4 ■ **Approximate Fetal Radiation Exposures during Selected Radiologic Studies**

Study	Millisieverts (rem)
Chest radiograph	<0.01 (<0.001)
Abdominal radiograph (single exposure)	0.4 (0.04)
Barium enema	20–40 (2–4)
Abdominal CT scan (10 slices)	20 (2)
Pulmonary $\dot{V}/\dot{Q}$ scan (technetium^{99m})	<0.5 (<0.05)
Contrast venography (lower extremity)	6 (0.6)

TABLE 28.5 ■ **Indications for Continuous Fetal Heart Rate Monitoring in the Intensive Care Unit**

Indications	Examples
Maternal hypoxemia	Acute severe asthma attack
Maternal hypovolemia	Hemorrhage
Maternal hypertensive crisis	Severe preeclampsia
Postoperative states	Effects of anesthetic agents on fetal heart rate
	Increased risk for preterm delivery after laparotomy
Fetal indications	Preterm labor

Continuous fetal heart rate monitoring should not be considered until the fetus has reached the threshold of viability (24 weeks of gestation in most institutions). This technology requires frequent interpretation by qualified obstetric personnel. Intermittent fetal heart rate assessment may be performed using hand-held Doppler ultrasonography after 12 weeks of gestation. Although improved fetal outcome has not been proved, intermittent electronic fetal monitoring is recommended for all hospitalized obstetric patients before 24 weeks of gestation.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 29

Care of the Patient with Morbid Obesity

Joshua Diamond ■ William Schweickert

As the prevalence of overweight and obesity continues to increase, efforts have been made to quantify this weight change in individuals. Overall body fat cannot be measured directly. Body weight provides an indirect measure of fat stores; however, variable body build and composition prevent delineation of ideal body weight. The measurement most often used to quantify body fat is body mass index (BMI). Easily calculated as weight in kilograms divided by height in meters squared, BMI closely correlates with body fat in most people and has defined risk categories. Specifically, according to the definitions used by Centers for Disease Control and Prevention (CDC), individuals with a measured BMI > 25 kg/m^2 are "overweight," ≥ 30 have obesity, and > 40 have "morbid obesity" (also referred to as "severe or extreme obesity)."

Background/Epidemiology

Worldwide at least 1 billion people are overweight, and more than 300 million are obese. The United States is experiencing an epidemic of obesity. The national health surveys conducted in 2009-2010 estimated more than one third of the adult U.S. population (about 78 million) as obese and virtually guarantee the presence of obese patients in the intensive care unit (ICU). The critically ill obese patient presents unique challenges that must be understood and anticipated to ensure optimal delivery of care (Table 29.1).

Respiratory Effects of Obesity

Obesity produces a wide range of effects on the respiratory system. The magnitude of these effects depends on three factors:

1. The severity of the obesity (morbid obesity has a near-universal impact)
2. The distribution of the body fat (central, abdominal adiposity adversely affects pulmonary mechanics more than other distributions)
3. Compensatory respiratory muscle strength

The most commonly encountered pulmonary function change is a decrease in the expiratory reserve volume (ERV), ascribed to the cephalad displacement of the diaphragm by adipose tissue (Figure 29.1). Other frequent changes include increases in the ratio of the forced expiratory volume in one second (FEV_1) to the forced vital capacity (FVC; ratio: FEV_1/FVC). As obesity becomes extreme, lung volumes can become more deranged with low total lung capacity (TLC), vital capacity (VC), and functional residual capacity (FRC). As expected, the respiratory system compliance is decreased, from the mechanical effects of the adipose tissue on the thoracic cage (chest wall restriction), and also on lung compliance from the reduced FRC with dependent atelectasis. Interestingly, residual volume (RV) may be increased relative to TLC (i.e., RV/TLC ratio), reflecting a reduction in small airway caliber and susceptibility

TABLE 29.1 ■ **Effects of Obesity on Organ Systems**

Organ System	Effects of Obesity
Respiratory	Decreased ERV, TLC, VC, FRC
	Decreased compliance (both chest wall and respiratory)
	Increased $\dot{V}O_2$ and $\dot{V}CO_2$
	Increased air trapping
	Widened A-a gradient ($PAO_2 - PaO_2$) (Chapter 1)
Cardiovascular	Increased cardiac output
	Chronic volume overload
	Left ventricular hypertrophy and diastolic dysfunction
	Systemic and pulmonary hypertension
Renal	Microalbuminuria
	Glomerular hyperfiltration
	Increased renal blood flow
Hepatobiliary	Increased risk of cholesterol gallstones
	Increased risk for NAFLD, NASH
Endocrine	Increased risk for diabetes, insulin resistance
	Increased risk for dyslipidemia

ERV, expiratory reserve volume; TLC, total lung capacity; VC, vital capacity; FRC, functional residual capacity; $\dot{V}O_2$, oxygen consumption; $\dot{V}CO_2$, carbon dioxide production; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

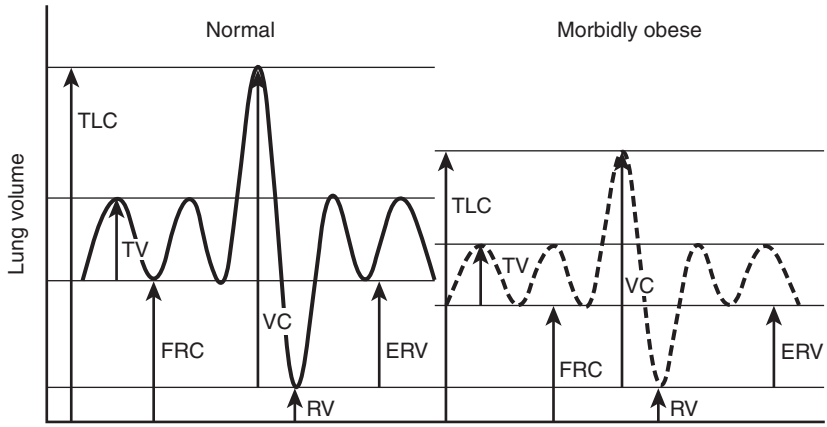


Figure 29.1 Schematic spirograms that compare lung volumes and capacities between normal-weight patients (solid line) and morbidly obese patients (dashed line). TLC, total lung capacity; VC, vital capacity; FRC, functional residual capacity; RV, residual volume; TV, tidal volume.

to premature airway closure, precipitating gas trapping. Furthermore, evidence implicates increased rates of asthma in the obese population.

The respiratory system derangements produced by obesity are exacerbated by the supine position of a critically ill patient. The maximal displacement of the diaphragm and added weight of the chest cause peripheral airway closure in dependent lung regions (atelectasis), resulting in mismatch of ventilation and perfusion. This ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch creates a widened alveolar to arterial oxygen gradient (PAo_2-Pao_2), along with typically mild to moderate

hypoxemia. Severe hypoxemia may be present, however, in individuals with the obesity hypoventilation syndrome (as a result of the additional contribution of hypoventilation; see Chapter 80) or in the postoperative patient (especially following thoracic and upper abdominal surgeries; see Chapter 90). Even severe hypoxemia may present with a relatively unremarkable chest radiograph, or perhaps minimal basilar atelectasis.

An elevated work of breathing predisposes obese patients with critical illness to respiratory failure. At baseline, obese patients have a high oxygen consumption ($\dot{V}O_2$), although oxygen consumption *per kilogram* is somewhat reduced given the relatively low metabolic rate of adipose tissue. Furthermore, the fraction of oxygen consumption related to the work of breathing is very high, from highly inefficient respiratory muscle function. Therefore, morbidly obese patients should be viewed as manifesting chronic ventilatory failure in which relatively small additional increases in $\dot{V}O_2$ or carbon dioxide production ($\dot{V}CO_2$) (i.e., from sepsis or respiratory compensation for metabolic acidosis) precipitate acute hypercapnic respiratory failure (Chapter 1).

Cardiovascular Effects of Obesity

The circulatory derangements attributed to obesity can be quite difficult to appreciate. The usual markers of volume status (neck vein assessment, precordial impulse, distal pulses), chest radiographs, electrocardiograms, and even blood pressure measurements (appropriate cuff sizing) can all be limited. Therefore, maintain a high clinical suspicion for ventricular dysfunction and pulmonary hypertension.

Cardiac output is increased in obesity from increased extracellular volume and blood flow to most tissue beds, mediating increased preload and cardiac dilation. This chronic volume-overload state, either in isolation or combined with increased left ventricular afterload from concurrent systemic hypertension, may result in marked left ventricular hypertrophy, further impairing ventricular filling and resulting in diastolic heart failure.

Systolic dysfunction may also result from this chronic pressure overloaded state (long-standing hypertension) or from ischemic heart disease. The risk of death from cardiovascular disease rises steeply above a BMI of 30 kg/m^2. Obesity increases the risk of coronary and other atherosclerosis from a myriad of parallel risk factors including hypertension, insulin resistance, and dyslipidemia.

Pulmonary hypertension with right ventricular hypertrophy and dilation may accompany obesity. When not caused by left ventricular failure, pulmonary hypertension in obese patients typically arises from sustained hypercapnia and hypoxemia (because of obesity hypoventilation [Chapter 80] or concomitant chronic obstructive pulmonary disease), eliciting pulmonary vasoconstriction. Absent effective therapy (weight loss, nocturnal invasive or non-invasive ventilation, supplemental oxygen), such pulmonary hypertension can produce cor pulmonale.

Other Organ System Manifestations

Obesity is associated with progressive renal insufficiency. Microalbuminuria combined with increased renal blood flow and elevated glomerular filtration rate are frequently present in obesity, subsequently leading to glomerular sclerosis in a manner analogous to diabetes. Beyond the direct effects of obesity on the kidney, concomitant diabetes and hypertension account for a significant proportion of cases of end-stage renal disease in this population.

The hepatobiliary system endures damages as well. Obesity is a well-established risk factor for cholesterol gallstones, increasing the likelihood of biliary sepsis and gallstone pancreatitis. Multiple studies reveal obese subjects have ultrasonographic evidence of fatty liver, and 30% of these patients have documented nonalcoholic steatohepatitis (NASH) that may progress to cirrhosis. The degree of obesity parallels the likelihood for both fatty liver and NASH.

Implications for Management

AIRWAY

Endotracheal intubation in obese critically ill patients can be difficult because of limited neck mobility, reduced mouth opening, and short sternomental distance. Not BMI alone, but large neck circumference and a Mallampati score of 3 or more (Chapter 80) are significantly correlated with a high probability of problematic intubation. Further, the supine position for intubation may precipitate significant airway closure and potential arterial oxyhemoglobin desaturation, a situation minimally responsive to bag-mask ventilation. Reasonable approaches include the ramped position coupled with awake intubation when laryngeal structures cannot be visualized, and rapid sequence intubation for the remaining obese patients. The high risk of aspiration in this population during intubation emphasizes the importance of cricoid pressure and other measures during intubation (Chapter 30).

In the event of a need for tracheostomy, an experienced surgeon is necessary. There remains debate regarding the safety of percutaneous dilatational tracheostomy, the need for custom-fit tracheostomy tubes, and tracheotomy techniques that remove cervical fat (Chapters 22 and 30). Beyond the usual indications, tracheostomy should be anticipated early in the patient with severe obesity hypoventilation syndrome with baseline daytime hypercapnia and hypoxemia (Chapter 80).

BREATHING

Efforts should always be directed to avoid atelectasis and hypoventilation in the obese. Treatments include adequate analgesia while avoiding oversedation, early mobilization, vigorous pulmonary toilet, and upright positioning. The simple maneuver of upright or reverse Trendelenburg positioning improves respiratory system compliance, closing volume, and, most significantly, oxygenation.

One should consider non-invasive ventilation in the patient with known or suspected sleep-disordered breathing, especially as first-line therapy for respiratory failure (Chapter 3). Non-invasive ventilation unloads the respiratory muscles, decreases atelectasis, and addresses sleep-disordered breathing while maintaining an interactive patient. Although effective, one should carefully consider the risk of aspiration with this therapy.

Despite such measures, rapidly deteriorating respiratory failure in the obese may require intubation and mechanical ventilation. Severe hypoxemia and hemodynamic decompensation following intubation frequently occur. Anticipation of these difficulties is paramount, and measures should include early central venous access, vasoactive drug availability aimed at underlying cardiac dysfunction, upright positioning, and judicious application of positive end-expiratory pressure. Low tidal volume ventilation strategies (i.e., 6 mL/kg predicted body weight [PBW]; Table 29.2), a mainstay of treatment for acute lung injury (ALI) and acute respiratory distress (Chapter 73), can be challenging to implement in this population. An elevated plateau pressure, reflecting the compliance of the respiratory *system* (including both lungs and chest wall), may better reflect the weight of the chest wall rather than the presence of alveolar overdistention. Some authors argue that obesity is protective in this manner. To try to decrease the effects on respiratory system compliance caused by abdominal contents, it may be helpful to consistently measure the plateau pressure in a (semi)upright position and permit plateau pressures up to 35 cm H_2O with 6 mL/kg PBW in the morbidly obese. Although beneficial to those patients with ALI, low tidal volumes have not been proven beneficial in other etiologies of respiratory failure in the morbidly obese and can be expected to promote further atelectasis, thereby worsening oxygenation.

Similarly, meeting criteria for extubation may be difficult because at baseline obese patients may demonstrate elevated positive end-expiratory pressure (PEEP) needs, marginal oxygen saturations, and shallow breathing patterns. Clinicians should utilize upright positioning, sedation sparing strategies, and postextubation non-invasive ventilation to address these obstacles.

TABLE 29.2 ■ **Dosage of Selected Drugs According to Total, Adjusted, or Predicted Body Weight**

Dosed by Total Body Weight (TBW)	Dosed by Adjusted Body Weight (ABW)	Dosed by Predicted Body Weight (PBW)*
Vancomycin	Aminoglycosides[4]	H_2-blockers
Daptomycin	Quinolones[5]	Digoxin
Quinupristin-dalfopristin		Phenytoin maintenance dose
Atracurium		Flucytosine
Succinylcholine		Ethambutol
Rocuronium		Pyrazinamide
Diazepam loading dose		Theophylline
Lorazepam loading dose		Vecuronium
Midazolam loading dose		Diazepam maintenance dose
Phenytoin loading dose[1]		Lorazepam maintenance dose
Lithium		Midazolam maintenance dose
Carbamazepine		Propofol
Valproic acid		
Unfractionated heparins[2]		
Low-molecular-weight heparins (LMWH)[2,3]		

*Predicted body weight (PBW): Males: (kg) = 50 + 2.3 (height [in] – 60); Females: (kg) = 45.5 + 2.3 (height [in] – 60).
[1]2 g loading dose maximum.
[2]Dosages include loading and maintenance dose caps.
[3]Follow Factor Xa levels when weight > 150 kg.
[4]Adjusted body weight for aminoglycosides = PBW + [0.4(TBW – PBW)].
[5]Adjusted body weight for ciprofloxacin = PBW + [0.45(TBW – PBW)].

CIRCULATION

Hypotension in the critically ill, obese patient creates a lethal scenario. The usual approach to shock applies, including assessment of pulse pressure, neck veins, and extremity perfusion. However, markers of volume status are obscure in the obese, and central venous pressures may be difficult to interpret in the setting of unclear right ventricular function. As a result, more sophisticated measures of volume status are necessitated, including measurements of respiratory variation in central venous pressure, arterial pulse pressure variation, and further diagnostic testing including transesophageal echocardiography and right heart catheterization.

Once euvolemia or hypervolemia is established, the best vasoactive drugs are generally norepinephrine or dobutamine. Norepinephrine is the vasopressor of choice in the hypotensive patient, able to provide inotropy, mobilization of the unstressed volume, and cardiac perfusion in the acute right heart syndrome. Some clinicians prefer dobutamine in patients with a relatively subacute decompensation, suspected/known right heart dysfunction, and adequate perfusion pressure.

VENOUS THROMBOEMBOLIC DISEASE

Obesity comprises a risk factor for venous thromboembolism (VTE) via inactivity, venous stasis, and hypercoagulability. The usual recommendations for thromboembolism prophylaxis of acutely ill hospitalized patients, including the use of either low-dose unfractionated heparin or low-molecular-weight heparin, should be applied to the obese population (Chapter 12).

Finally, given this high-risk category, all obese patients with respiratory failure (with or without hemodynamic compromise) should have the diagnosis of pulmonary embolism entertained (Chapter 77).

VASCULAR ACCESS

Obtaining central venous access in critically ill, morbidly obese patients can be challenging. Obscure anatomic landmarks, superficial candidal intertriginous fungal infections, and increased depth of insertion necessary to gain venipuncture access contribute to the high risk and difficulty. Ultrasound-guided internal jugular cannulation is the preferred central venous access. One should consider early use of a peripherally inserted central catheter (PICC) in obese patients with access difficulties. Femoral cannulation should generally be performed as a last resort. Meticulous evaluation for catheter site infections should be conducted, as indwelling catheters are kept in place longer in obese patients when compared to normal-weight patients, attributed to difficulty finding alternative peripheral intravenous (IV) access.

NURSING CARE

The critically ill obese patient may be difficult to mobilize, multiplying the risk for pressure ulcers and vascular stasis–induced thromboembolic disease. Deep sedation prevents the assistance of patient movement. Improved bariatric beds with pressure relief features reduce the development and severity of pressure ulcers (Chapter 42). Hydraulic lifts and hoists with appropriate-sized slings can improve adherence to mobility and turning goals. Both the decreased vascularity of adipose tissue impairing wound healing and the frequency of fungal infections in the intertriginous regions necessitate diligent skin care. The number of nurses required to care for morbidly obese patients far exceeds that required for normal-weight patients.

NUTRITIONAL REQUIREMENTS

Despite excess body fat stores, the morbidly obese develop protein calorie malnutrition during metabolic stress. Compared to the nonobese, these patients mobilize more protein and less fat, partly explained by elevated basal insulin levels. The preferential use of carbohydrates results in greater protein breakdown, mediating loss of lean muscle mass and potential adverse effects on immune function and wound healing. While indirect calorimetry is the method of choice to determine energy expenditure if the inspired oxygen is < 60% (Chapter 15), the Harris-Benedict equation can estimate basic metabolic needs using total body weight (TBW) (Chapter 15).

Accumulating data support the use of enteral, hypocaloric, high-protein feeding for the critically ill obese patient. In these studies, the average nonprotein caloric intake was 11 to 14 total kcal/kg TBW per day or 22 to 25 total kcal/kg PBW per day, and the average protein intake was 1.5 to 2.1 g/kg PBW per day. Various studies of such a diet have shown shorter ICU length of stay, shorter duration of antibiotic use, a trend toward a decrease in the number of ventilator days, and improved glycemic control. The difficulty in determining the adequate caloric intake for patients with obesity highlights the importance of the dietician or nutritional support consultation in the critical care setting.

PHARMACOKINETICS

Pharmacokinetics are hard to predict in the obese; increased volume of distribution, fat storage, and glomerular filtration rate, combined with alterations in plasma binding proteins, preclude simple rules of drug dosing (Chapter 17). Drugs with a narrow therapeutic window, such as

theophylline and digoxin, may result in toxicity when dosed according to total body weight. Reference to published guidelines for individual drugs is recommended; however, one can categorize dosing regimens based on adherence to TBW, adjusted body weight, PBW, and those that require plasma level monitoring (Chapter 17 and Table 29.2).

Some examples are worthy of specific mention. The volume of distribution and clearance of vancomycin better correlates with a patient's actual body weight compared to PBW. Furthermore, the drug's half-life is shorter in morbidly obese patients, necessitating a shorter interval between doses. Propofol, frequently used in the ICU for induction and maintenance of anesthesia as well as sedation (Chapter 5), should be dosed by PBW in the morbidly obese as opposed to total body weight.

Bariatric Surgery and Postoperative Critical Care

Morbidly obese patients unable to lose weight with diet and exercise alone may undergo surgical treatment for their obesity (Chapter 93). Restrictive procedures such as vertical banded gastroplasty have high rates of anastomotic leak, whereas laparoscopic adjustable gastric banding has a lower rate of complications but produces less sustained weight loss. Malabsorptive procedures including sleeve gastrectomy and Roux-en-Y gastric bypass may also be complicated by anastomotic leaks but produce higher sustained weight loss.

Approximately 20% to 25% of postoperative bariatric surgery patients require ICU care, most often for prolonged mechanical ventilation and anastomotic leaks. Although overall mortality rates for bariatric surgery in the United States are between 0.24% to 0.4%, one case series of bariatric surgical patients requiring postoperative intensive unit care revealed a mortality of 2.9% in this subgroup. Risk factors for postoperative ICU care and prolonged mechanical ventilation (> 24 hours) include BMI ≥ 60 and the need for reoperation.

Many institutions have developed clinical algorithms for patients undergoing bariatric surgery, including the universal use of venous thromboembolic prophylaxis (Chapter 77) and early institution of non-invasive ventilation (Chapter 3). However, no evidence-based guidelines currently exist for preoperative triage of patients to ICU-level care; in most institutions, triage is done on a case-by-case basis.

Obesity and Outcomes from Critical Illness

Fortunately, despite the aforementioned obstacles caring for the critically ill, obese patient, ultimate clinical outcomes do not appear worse, with some exceptions. In general, large-scale studies reveal no significant difference in mortality, even in the most extreme obese (BMI > 60), after controlling for confounders. However, studies do identify increased ICU length of stay, mechanical ventilator days, and total length of stay in the most obese patients when compared to nonobese patients. One notable exception was the significantly increased risk of death of obese patients (odds ratio [OR] = 3.1) and morbidly obese patients (OR = 7.6) compared to normal-weight adults hospitalized for H1N1 influenza in 2009. Another important exception is the increased risk of morbidity and mortality that patients with morbid obesity have when undergoing bariatric and other major abdominal surgery (Chapter 93).

An annotated bibliography can be found at www.expertconsult.com.

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Burns SM, Egloff MB, Ryan B, et al: Effect of body position on spontaneous respiratory rate and tidal volume in patients with obesity, abdominal distention and ascites. Am J Crit Care 3:102-106, 1994.

In patients with abdominal distention, ascites and obesity, reverse Trendelenburg position at 45 degrees produces larger spontaneous tidal volumes and lower respiratory rates compared with the 90 degree (seated) position.

Collins JS, Lemmens HJM, Brodsky JB, et al: Laryngoscopy and morbid obesity: a comparison of the "sniff" and "ramped" positions. Obes Surg 14:1171-1175, 2004.

This observational trial demonstrated that the ramped position (elevating upper chest and head until external auditory meatus was level with sterna notch) provided superior laryngeal views than the "sniff" position (blanket elevating head a standard height above operating room table) for morbidly obese patients undergoing intubation for bariatric surgery.

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In this matched cohort study of severely obese patients, immediate post-extubation application of noninvasive ventilation reduced the rate of extubation failure and the duration of ICU and hospital lengths of stay.

Frat-J-P Gissot V, Ragot S, et al: Impact of obesity in mechanically ventilated patients: a prospective study. Intensive Care Med 34:1991-1998, 2008.

This multicenter, matched cohort prospective study found no difference in mortality between obese and non-obese mechanically ventilated patients but demonstrated increased difficulty with intubation and higher incidence of post-extubation stridor.

Hogue CW Jr, Steans JD, Colantuoni E, et al: The impact of obesity on outcomes after critical illness: a meta-analysis. Intensive Care Med 35:1152-1170, 2009.

This meta-analysis demonstrated no difference in ICU mortality, but lower hospital mortality, for obese and morbidly obese versus normal weight patients. There was no association between obesity and duration of mechanical ventilation or length of ICU stay.

Honiden S, McArdle JR: Obesity in the intensive care unit. Clin Chest Med 30:581-599, 2009.

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This provides a recent perspective on obesity prevalence trends in the United States.

CHAPTER 30

Airways and Emergency Airway Management

Benjamin K. Scott ■ Maurizio Cereda ■ Erica R. Thaler ■ Kelly M. Malloy

Airway management is an essential skill for the intensivist. A secure, patent airway facilitates respiratory gas exchange and clearance of orotracheal secretions, limits aspiration of orogastric contents, and can provide a route for the administration of humidified gases and some medications. Although the patient's own anatomic airway may be sufficient to meet these needs, in the context of critical illness, invasive and non-invasive airway management techniques are often required. This encompasses familiarity with the equipment and standard techniques used for bag-valve mask ventilation, endotracheal (ET) tubes (Figure 30.1), ET intubation, and the pharmacologic agents that may be required to accomplish these maneuvers (Tables 30.1 and 30.2).

Emergency airway management in the intensive care unit (ICU) setting is potentially more technically difficult and hazardous than airway management in the elective setting. The *difficult airway* has been defined as the clinical situation in which a skilled operator experiences difficulty with mask ventilation, tracheal intubation, or both. When confronted with either an anticipated or unanticipated difficult airway, the intensivist should be familiar with methods of advanced or "rescue" airway management, including fiberoptic bronchoscopic intubation, laryngeal mask airway (LMA) or other blind-insertion devices, and emergent surgical airway access. Generally accepted predictors of difficult mask-ventilation or ET intubation are presented in Box 30.E1.

Finally, the intensivist must be able to diagnose and resolve common and potentially life-threatening airway complications, including, but not limited to, mainstem or esophageal intubation, ET cuff leak or cuff herniation, ET tube obstruction, tracheostomy bleeding, and inadvertent extubation or decannulation.

Useful Drugs in Emergency Airway Management

Favorable conditions for airway management require judicious use of a variety of medications. Local anesthetics, sedative hypnotics, analgesics, and neuromuscular blockers in standard concentrations or prefilled syringes should be readily available in the ICU.

LOCAL ANESTHETICS

Topical application or infiltration of local anesthetics can blunt airway reflexes and facilitate awake or semi-awake fiberoptic intubation by the oral or nasopharyngeal route. Lidocaine is used most commonly and is often combined with a vasoconstrictor designed to constrict mucosal blood vessels and minimize bleeding. Local anesthetics may be delivered topically using a standard nebulizer, a curved atomizer, an aerosol spray, or via soaked pledgets. The glossopharyngeal and laryngeal nerves may also be blocked by local infiltration, and the upper airways may be anesthetized

Additional online-only material indicated by icon.

BOX 30.E1 ■ Risk Factors Associated with a Difficult Airway

Abnormalities with Normal Facial Anatomy

- Small mouth or large tongue
- Maxillary prognathia
- Acromegaly
- Severe dental abnormalities
- Facial trauma
- Congenital anomalies (e.g., Treacher Collins syndrome)

Abnormalities with Pharyngeal or Laryngeal Anatomy

- Soft-tissue swelling (e.g., pregnancy, superior venacaval [SVC] syndrome)
- Anterior larynx
- Deep vallecula
- Tissue or structural distortion (e.g., tumor, previous irradiation, prior tracheostomy)
- Subglottic stenosis

Abnormal Mouth Opening

- Temporomandibular joint dysfunction
- Radiation fibrosis
- Mechanical obstruction (e.g., surgical wires, facial trauma)
- Facial burns
- Scleroderma
- Masseter muscle spasm (dental abscess)

Abnormal Cervical Mobility

- Short neck
- Inflammatory diseases (e.g., ankylosing spondylitis)
- Prior surgery of cervical spine
- Concern for cervical injury (need to maintain immobility with c-collar)
- History of difficult airway

Adapted from Lavery GG, McCloskey BV: The difficult airway in adult critical care. Crit Care Med 36:2163-2173, 2008.

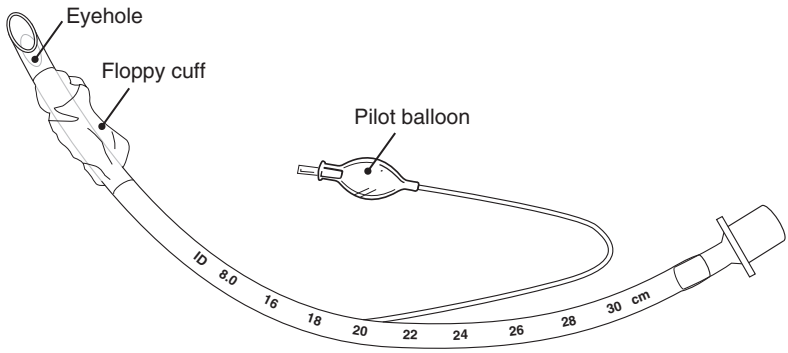


Figure 30.1 Typical polyvinyl chloride ET tube with a low pressure, high-volume, high-compliance ("floppy") cuff connected to a pilot balloon. Distance from the tip of the tube is marked in centimeters; these can guide the depth of initial tube placement (proper depth, when secured at the corner of the mouth, is ~21 cm for adult women and ~23 cm for adult men) and subsequently when the tube is moved and resecured in the mouth. The side-opening (eyehole) near tip of tube provides additional path for air entry if the main lumen becomes occluded.

TABLE 30.1 ■ **Selected Agents to Facilitate Endotracheal Intubation in the Intensive Care Unit**

Agent	Class	Dose	Comments
Sodium thiopental	Hypnotic (barbiturate)	1–5 mg/kg	Dose-dependent effects of myocardial depression and peripheral vasodilation; causes hypotension; Relative contraindication in patients with even mild volume depletion, shock, or congestive heart failure
Etomidate	Hypnotic (benzylimidazole)	0.3–0.6 mg/kg	Has fewer hemodynamic effects than sodium thiopental; provides no analgesia; suppresses cortisol release; myoclonus occurs in approximately 30%; relative contraindication in patients with moderate volume depletion or pregnancy
Propofol	Hypnotic (alkylphenol)	1–2.5 mg/kg	Give only half the dose for elderly, debilitated, or critically ill patients; may cause profound hypotension in hypotensive or hypovolemic patients
Ketamine	Dissociative anesthetic	1–2 mg/kg	Depresses myocardium but can preserve blood pressure by sympathetic stimulation; emergence reactions occur in approximately 12%; preserves pharyngeal and laryngeal reflexes; relative contraindication in patients with moderate volume depletion or increased intracranial pressure
Fentanyl	Opioid	1–3 μg/kg	Provides sedating effects without amnesia; may cause hypotension; does not blunt hypertensive reflex to endotracheal intubation; patients previously exposed to opioids will generally need higher doses
Midazolam	Benzodiazepine	20–100 μg/kg	Can cause hypotension when given in high doses, with other agents (opioids), or in hemodynamically unstable patients; patients previously exposed to this class of agent will generally need higher doses

TABLE 30.2 ■ **Neuromuscular Blocking Agents Used for Endotracheal Intubation in the Intensive Care Unit**

Agent	Class	Dose	Comments
Succinylcholine	Depolarizing	1–2 mg/kg	Profound paralysis lasting 5–10 min in normal individuals; releases potassium from skeletal muscle (serum potassium rises by 0.5–1.0 mEq/L in normal individuals); severe hyperkalemia with cardiac arrest may occur in patients with massive trauma, burns, lower extremity paralysis or denervated states (multiple sclerosis), or muscular dystrophies
Pancuronium	Nondepolarizing	0.1 mg/kg	Rapid onset; long acting; likely to cause tachycardia (may be severe); active metabolite accumulates in renal failure and can cause prolonged paralysis
Vecuronium	Nondepolarizing	0.1 mg/kg	Rapid onset; short-to-intermediate duration of action; negligible hemodynamic effects; active 3-desacetyl metabolite accumulates in renal failure and can cause prolonged paralysis
Cisatracurium	Nondepolarizing	0.15–0.2 mg/kg	Intermediate onset; short duration of action; no effects on nicotinic, autonomic receptors or muscarinic cardiac receptors; may cause histamine release when given rapidly in high dosage;
Rocuronium	Nondepolarizing	0.6–1.2 mg/kg	Rapid onset (can be used for rapid sequence intubations when succinylcholine is contraindicated); intermediate duration of action; primarily metabolized by liver with minimal pharmacokinetic changes seen in renal failure; minimal effects on heart rate or blood pressure

using a transtracheal approach. Alternatively, the injection port of the bronchoscope may be used to deliver local anesthetic agents directly to the larynx as the scope is advanced into the airway.

Safe use of local anesthetics depends on their proper dosing, appropriate administration, knowledge of maximum allowed dose, and signs of toxicity. Early signs of overdose include a metallic taste in the mouth and tinnitus. Higher doses may precipitate seizures or intractable cardiac arrhythmias.

ANTICHOLINERGIC AGENTS

Anticholinergic drugs, including atropine, glycopyrrolate, and scopolamine, are antisialagogues and may be used to help diminish secretions during awake intubation. Atropine and glycopyrrolate lack significant sedative properties but may cause tachycardia. Scopolamine has amnestic as well as sedating properties because it readily crosses the blood-brain barrier.

HYPNOTIC AGENTS, SEDATIVES, AND NEUROMUSCULAR BLOCKERS

A variety of hypnotic agents, commonly used to induce general anesthesia in the operating room, can also be used to facilitate ET intubation in the ICU. In general these agents are selected

for their rapid onset and short duration of action. Key properties and doses are presented in Table 30.1. To varying degrees, all of these agents can worsen hypotension in critically ill patients who are in shock, receiving pressors, or severely hypovolemic. Other agents, such as fentanyl, ketamine, or midazolam, can be used in these clinical circumstances and are favored during conscious sedation for semi-awake intubation or bronchoscopy. In order to produce favorable intubating conditions, hypnotic induction agents are frequently used in conjunction with a neuromuscular blocker. Since its introduction in the 1950s, succinylcholine has been the agent of choice for emergency intubation because of its rapid onset and short duration of action. Rocuronium, which approaches the rapid onset of succinylcholine without its numerous adverse effects, has gained favor. Table 30.2 lists dosing, adverse effects, and clinical considerations for the use of neuromuscular blockers for intubation.

Gastric Aspiration Precautions

Patients requiring urgent or emergent intubation in the ICU may have a full stomach, and in the setting of trauma or critical illness nearly all patients will have delayed gastric emptying, impaired protective physiologic mechanisms, and diminished airway reflexes. Accordingly, precautions should be taken against the aspiration of orogastric contents. In patients considered to be at high risk for urgent intubation, enteric feeding should be postponed, and gastric tubes, if present, should be suctioned. To decrease gastric pH, some clinicians advocate prophylactic premedication with nonparticulate antacids or histamine-receptor antagonists. Metoclopramide, a dopaminergic antagonist that increases lower esophageal sphincter tone and stimulates upper gastrointestinal motility, may also be used to promote gastric emptying. First described by Sellick in 1961 and widely accepted despite limited data supporting its efficacy, the application of cricoid pressure has been advocated as a means of preventing passive regurgitation of gastric contents. Although randomized controlled trials are lacking, rapid sequence induction (RSI) has also gained widespread acceptance among U.S. anesthesiologists and emergency department (ED) physicians. The principal aim of RSI is to reduce the time interval between loss of consciousness and intubation of the trachea while avoiding positive pressure ventilation of the unprotected airway. Standard RSI includes preoxygenation with 100% oxygen, administration of a rapid-onset and preferably short-acting induction agent and neuromuscular blocker, application of cricoid pressure, and avoidance of positive pressure ventilation until inflation of the ET cuff. Many providers favor the use of a "modified RSI" in which a gentle postinduction positive pressure breath is provided prior to administration of neuromuscular blockade to demonstrate that mask ventilation will be possible.

Equipment for Emergency Airway Management

An ever-expanding arsenal of rescue devices and airway adjuncts are available for emergency airway management. The devices and equipment reviewed here should be familiar to every intensivist, and most should be immediately available in the ICU. It bears repeating, however, that effective use of these tools requires practical, supervised experience in the ICU, ED, trauma bay, or operating room.

TOOLS FOR MASK VENTILATION

Effective ventilation by face mask is a fundamental skill that every intensivist should master. Face mask ventilation may be lifesaving, but is sometimes underemphasized or taken for granted. Every patient room in the ICU should be stocked with a face mask and self-inflating (bag-valve mask) manual resuscitation bag that can be readily connected to wall oxygen.

Difficulty in achieving satisfactory mask ventilation, as evidenced by cyanosis, failure of chest rise, decreasing oxygen saturation, or the absence of end tidal CO_2, may be related to inadequate mask seal, obstruction of the patient's airway, or both. Repositioning the patient's head to achieve a sniffing position, applying a jaw thrust maneuver, or using a two-handed mask grip may improve conditions. Additionally, *oral* or *nasopharyngeal airways* may be inserted to maintain upper airway patency. Oral airways are particularly useful in relieving airway obstruction in obese or edentulous patients. These airways are made of hard plastic and should not be used as bite blocks, as their long-term use may cause lingual nerve injury. Nasopharyngeal airways are generally soft, flexible rubber and should be lubricated before insertion to prevent excessive nasopharyngeal trauma or bleeding. They are contraindicated in patients with coagulopathy or significant facial or skull-base trauma.

TOOLS FOR LARYNGOSCOPY

The modern laryngoscope consists of a standardized handle, a light source, and a curved or straight blade designed to displace the tongue, illuminate the larynx, and guide an ET tube through the vocal cords and into the trachea. Numerous blade designs have been introduced over the years. In adult patients, however, the Miller and MacIntosh blades remain the most commonly used. The long, straight, and relatively narrow Miller blade has a gently curved tip and is designed to elevate the epiglottis directly. Many operators prefer this blade in cases of limited mouth opening as it allows greater anterior displacement of the mandible. The MacIntosh blade is curved, wider, and has a perpendicular flange along the underside of the blade's left side, designed to sweep the tongue to the left and out of the operator's field of view. The tip of the MacIntosh blade is designed to rest in the vallecula, thereby elevating the epiglottis indirectly. Both blades are available in multiple sizes. Most adults can be intubated using a Miller 2 or MacIntosh 3.

Several rigid indirect laryngoscopes are also available. These devices transmit a close-up view of the glottis from the blade tip to an eyepiece or liquid crystal display (LCD) screen using fiberoptic technology. The principal advantage of these scopes is that they eliminate several of the variables that may result in difficult direct laryngoscopy. In particular, they allow indirect visualization of the vocal cords with minimal need to sublux the jaw or extend the neck. This may be particularly important in patients with limited mobility of the mandible or cervical spine.

In the case of a known or anticipated difficult airway, semi-awake flexible fiberoptic bronchoscopy is the technique of choice for many practitioners. Sedation is minimized to preserve spontaneous respiratory drive and airway reflexes are blunted by topical or local anesthetics. An ET tube is then loaded over a flexible fiberoptic bronchoscope, inserted into the oropharynx via oral airway or bite block, and advanced through the vocal cords using optical guidance. A combination of tip flexion and scope rotation allows three-dimensional navigation.

RESCUE AIRWAY DEVICES

The lightwand is a modified ET stylet that uses a small power source to illuminate the stylet tip. Because the trachea is an anterior, midline structure in the neck, the lighted tip will transilluminate the soft tissues of the neck in the midline when the stylet is in the trachea, but it will not be visible if it is placed in the esophagus. Like the indirect laryngoscopes, the lightwand can be used when mouth opening and neck extension are limited or contraindicated. A disadvantage is that the device does not allow for either direct or indirect visualization of the vocal cords and relies solely on the detection of light through the neck. Although some experienced users can also "feel" the wand as it glides over the tracheal rings, this device is less reliable than those that allow visualization of the glottic opening.

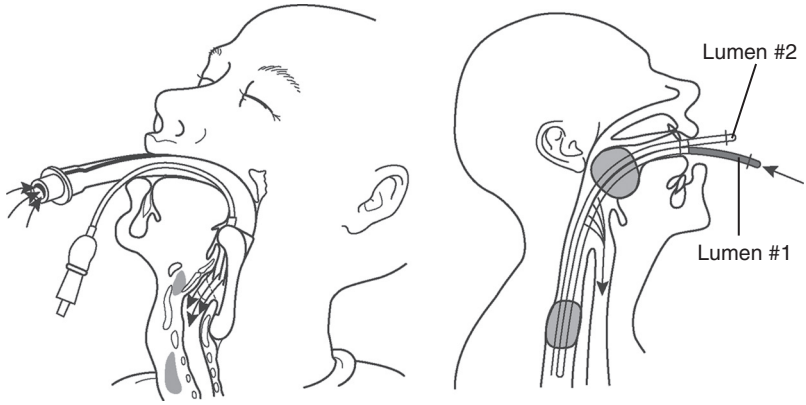


Figure 30.2 *Left panel*. The laryngeal mask airway (LMA) consists of an inflatable, elliptical-shaped mask ("cuff") that is positioned blindly within the hypopharynx and directs ventilation through slitlike apertures within the cuff and into the laryngeal inlet *(see arrows)*. A modified endotracheal tube is connected to the mask to enable delivery of positive pressure ventilation. There are numerous types of LMAs with various modifications, but all share the same basic functions. Importantly, patients who are at risk for gastric aspiration should not be managed for extended periods of time with an LMA because, by virtue of where it rests in the pharynx, aspirate can readily enter the trachea. *Right panel*. Combitube intubation. After blind insertion of a Combitube to the depth marked on the tube, the distal cuff is inflated. If the tube has entered the trachea (as drawn in the figure), inflation of the distal cuff, and ventilation through lumen #2 will lead to chest rise, capnographic color change, and the other indicators of tracheal intubation. If the tube is inserted into the esophagus, which is more likely, inflation of the distal cuff will not result in ventilation. In this case, the larger, proximal cuff should be inflated, thereby sealing the hypopharynx and allowing ventilation through lumen #1 using eyeholes positioned between the two cuffs.

Difficult laryngoscopy can often be overcome using an intubating bougie. This thin, semirigid rod has a slightly angled distal tip, which can be tucked under a partially visible epiglottis during laryngoscopy (similar to the lightwand) and then inserted blindly into the airway. The angled tip similarly creates a characteristic "washboard" sensation when advanced into the trachea as it skips over the anterior tracheal rings. An ET tube can then be advanced over the bougie, and the bougie withdrawn, leaving behind a secure airway.

The laryngeal mask airway, or LMA, consists of a curved single lumen tube that ends in an inflatable cuff designed to be placed into the oropharynx, covering the laryngeal inlet and creating a low-pressure glottic seal for positive pressure ventilation (Figure 30.2). They are available in several weight-based sizes. The LMA is placed blindly, requires relatively little manipulation of the head and mandible, and can be placed using significantly less sedation than ET intubation. Widely used for routine elective surgery, the LMA has also become invaluable as a rescue airway device because it allows for blind insertion and bypasses many of the anatomic features responsible for difficult mask ventilation or laryngoscopy, Following placement of an LMA and confirmation of adequate gas exchange, fiberoptic or blind ET intubation may be performed using the curved lumen of the LMA to guide an ET tube or Aintree intubation catheter into the trachea. Because it does not protect against aspiration and because the cuff may cause pressure necrosis after several hours, the LMA cannot be considered a definitive airway.

Other blind-insertion airway devices such as the Combitube and King airway device have found widespread acceptance by paramedics for emergent airway maintenance in the field. These devices consist of a dual lumen tube and two inflatable cuffs, one proximal (oropharyngeal) and one distal (esophageal or tracheal; see Figure 30.2). The King tube features a single inflation port and is designed to work with both cuffs inflated, regardless of tracheal or esophageal placement. Complications of these devices include upper airway hematoma and esophageal injury. Similar to the LMA, they should not be used for prolonged periods of time.

ENDOTRACHEAL TUBES

The modern ET tube is constructed from polyvinyl chloride and is available in numerous sizes and configurations (see Figure 30.1). Most feature a high-volume, low-pressure inflatable cuff designed to seal the trachea while exerting minimal pressure on the surrounding mucosa. The cuff is connected to a proximal pilot balloon, which allows inflation and deflation of the cuff with the tube *in situ*, and also facilitates estimation of cuff pressures. Distal to the cuff is an aperture commonly referred to as the Murphy eyehole, which is designed to allow gas flow even when the distal lumen is obstructed.

Standard ET tubes are preformed in a curvilinear shape designed to approximate the curvature of the natural airway. Preformed curves prevent kinking of the tube at points of flexion. Specialized, precurved RAE (named for inventors Ring, Adair, and Elwyn) tubes are available for nasotracheal intubation or oral intubations in which the ET tube must be flush with the chin to allow surgical access to the mouth or face. Another approach to the prevention of tube kinking has been the development of wire-reinforced tubes, which maintain their shape when flexed by incorporating a stainless-steel wire spiral. One must remember that these tubes may not be magnetic resonance imaging (MRI) compatible. Additionally, if they do become deformed (for example, if crushed by a patient's bite), they will retain the deformed shape.

Although most ET tubes are precurved, many practitioners prepare their tubes for intubation using an ET stylet. Stylets are rubber-coated, malleable segments of thick wire that can be inserted into the lumen of an ET tube and bent to maintain a preferred shape. Because the difficult-to-visualize larynx is often very anterior, many practitioners favor bending the distal tip of the stylet forward in the shape of a hockey stick. In emergency intubations, a stylet also provides additional stiffness that may be necessary to keep the ET tube from bending or collapsing during placement. To prevent laryngeal or tracheal injury, the stylet should never be allowed to protrude from the Murphy eye or extend beyond the tip of the tube.

Endotracheal tube size is determined by the internal diameter (ID) of the tube in millimeters. It is common practice to use a 7 to 7.5 mm ID (often referred to as #7 or #7.5) tube in an adult woman and a 7.5 to 8 mm ID tube in an adult man. Tubes > 7.5 mm can accommodate passage of a standard bronchoscope, but over time, larger tubes may also increase the risk of subglottic stenosis. Smaller diameter tubes may be indicated in the setting of laryngeal edema or tracheal stenosis, but these tubes provide increased resistance and may increase the work of breathing during weaning from the ventilator.

Confirmation of exhaled carbon dioxide, by capnography or colorimetric indicator, is the most reliable sign of a successful tracheal intubation and should be documented for every intubation. Unfortunately, even this is not 100% specific and false positives have been reported after esophageal intubation.

Proper depth of insertion is ~21 cm at the corner of the mouth for an adult woman and ~23 cm for a man. Most ET tubes are marked in 1-centimeter increments and have a radiopaque line enabling visualization on chest radiograph. The tip of the tube should be visible from 3 to 7 centimeters above the carina, or approximately overlying the T3 or T4 vertebral bodies. It is important to recognize that with flexion of the neck, an ET tube can move up to 2 cm toward the carina and 2 cm away with full extension. Tube position should be checked regularly by visual inspection, but in adults it does not mandate routine daily chest radiographs.

Although an inflated tracheal cuff protects the lungs from aspiration of large particulate matter, it does not prevent aspiration of liquids. One approach to this problem has been the development of ET tubes with subglottic suction ports. Some studies have shown reduced rates of ventilator-associated pneumonia with these tubes. One possible drawback to these tubes, however, is the potential for soft tissue injury when the subglottic port is left on continuous suction.

Obtaining a Secure Airway

ENDOTRACHEAL INTUBATION

Indications for ET intubation in the ICU include hypoxic or hypercapnic respiratory failure, impending respiratory failure from increased work of breathing, acute or progressive airway obstruction, and impending aspiration of gastric contents (usually a result of neurologic failure). Short-term intubations may also be necessary for the safe completion of diagnostic procedures, such as bronchoscopy or esophagoduodenoscopy. Non-invasive ventilation (Chapter 3) may be sufficient to treat some cases of respiratory failure and should be considered in the setting of obstructive sleep apnea, cardiogenic pulmonary edema, and hypercapnia resulting from chronic obstructive pulmonary disease (COPD). Non-invasive ventilation is not appropriate for long-term continuous ventilatory support and is contraindicated in patients who are at high risk for ongoing aspiration, those with active gastrointestinal bleeding, and patients with recent esophageal surgery or facial trauma.

Occasionally, one-lung ventilation may be necessary in the ICU. Bronchopleural fistula, massive unilateral hemoptysis, or unilateral lung abscess, for example, may require isolation of the affected lung. In these settings, intentional mainstem intubation may serve as a temporizing measure. Double-lumen ET tubes allow isolation and deflation of the right or left lung during thoracic surgery and are occasionally used to ventilate each lung independently in the ICU (e.g., in the setting of marked differences in compliance following single lung transplantation). These tubes are much larger than single lumen tubes with narrower lumens, however, and should not be used for extended periods. An alternative strategy for one-lung ventilation involves the placement of a bronchial blocker (see Figure 79.E1). Bronchial blockers utilize a high-volume, low-pressure cuff attached to a small-diameter tube that can be inserted through or parallel to the primary lumen of an ET tube and then inflated to seal off a main or segmental bronchus.

EMERGENT SURGICAL AIRWAY

In rare cases, ET intubation will be impossible despite the tools and techniques reviewed here. Rapidly progressive airway compromise or failed intubation complicated by an inability to ventilate using a face mask or rescue device necessitates emergent surgical access to the airway.

NEEDLE CRICOTHYROTOMY

Needle cricothyrotomy is a temporizing measure that involves the insertion of a large-bore angiocatheter through the cricothyroid membrane. Aspiration of air through the catheter suggests intratracheal placement. Ideally, the catheter is then connected to a wall oxygen source at 50 psi using a jet ventilation adapter, which allows for short bursts of high flow oxygen. If this device is not available, the catheter can be connected to a bag-valve mask using the connector from a 7 ET tube inserted into the back of a plungerless 3 mL Luer-lock syringe. Alternatively, a plungerless 10 mL or 20 mL Luer-lock syringe can be attached to the catheter, a cuffed ET tube inserted into the back of the syringe, and the cuff inflated to create a seal. Use of a bag-valve mask to deliver positive pressure through the angiocatheter will provide oxygenation, but ventilation will be dependent on passive recoil of the chest, and if the airway is obstructed proximally, ventilation will be impossible. If jet ventilation is not available, surgical cricothyrotomy should be performed immediately.

SURGICAL CRICOTHYROTOMY

In adult patients, surgical cricothyrotomy is the first-line emergency surgical approach to the airway. Emergent tracheotomy has a higher complication rate than elective tracheotomy, mostly

Although most intubations can and should be accomplished via the orotracheal route, nasotracheal intubation may be indicated in cases of dental, mandibular, or maxillary pathology. If laryngoscopy is not contraindicated, a nasally placed tracheal tube can be directed into the trachea during direct laryngoscopy using Magill forceps. Blind nasotracheal intubation can be performed in the spontaneously breathing patient with minimal sedation and provides an alternative approach to the anticipated difficult airway. In this technique, the nasal passages are lubricated and often pretreated with topical lidocaine for analgesia and phenylephrine or oxymetazoline for vasoconstriction. A tracheal tube is then advanced through the nose, with the bevel facing away from the septum, until breath sounds are audible in the tube. With inspiration, the tube is then advanced blindly. Tracheal placement is suggested by coughing, loss of vocalization, and persistence of breath sounds in the tube as it is advanced. If tracheal placement fails, small adjustments are made to the angle of approach by rotating the tube slightly or gently manipulating the larynx or head position of the patient. As always, tracheal intubation should be confirmed using capnography or colorimetric end-tidal CO_2 detection. As with nasogastric tube placement, coagulopathy, midface or basilar skull fractures, and recent sinus or sphenoid surgery are contraindications to nasotracheal intubation.

attributable to anatomic variables that are avoided by accessing the airway at the cricothyroid membrane. This more cephalad approach reduces the likelihood of mediastinal injury and pneumothorax, and because the cricoid and laryngeal cartilages are circumferential, reduces the risk of esophageal injury. After manual stabilization of the larynx, a 3- to 5-cm midline vertical or horizontal incision is made through the skin and subcutaneous tissues. The cricothyroid membrane is then perforated with the scalpel and spread open using a Trousseau dilator or curved hemostat. A #6 cuffed Shiley tracheostomy tube (or equivalent), if available, or a #6 cuffed ET tube is then inserted into the trachea and placement confirmed using standard methods. Alternatively, a needle cricothyrotomy may be performed and a guide wire advanced into the airway, allowing cannulation of the trachea by a series of dilators and finally the tracheostomy tube using a Seldinger technique. Commercially available kits have been developed for this purpose.

Compared with tracheotomy, prolonged cricothyrotomy is thought to increase the risk of subglottic stenosis, as well as vocal cord or laryngeal injury. Conventional teaching recommends conversion of all emergent cricothyrotomies to tracheotomy as soon as possible.

TRACHEOTOMY

Elective tracheotomy is also performed in ICU patients with long-term upper airway obstruction and those who are expected to require prolonged mechanical ventilation (see also Chapter 22). The optimal timing for this procedure remains unclear. The development of modern high-volume, low-pressure ET cuffs have reduced the incidence of tracheal stenosis from prolonged ET intubation. However, conversion to tracheotomy in patients who do not meet criteria for extubation in one to two weeks improves patient mobilization, reduces sedation requirements, and facilitates weaning from the ventilator by reducing airway resistance and dead space. Although early tracheotomy has not been consistently demonstrated to improve outcomes, it does appear to improve patient comfort compared to leaving an ET tube in place.

Tracheotomy may be performed at the bedside or the operating room using a standard surgical approach, in which a midline incision is made through the platysma, along the midline raphe of the strap muscles. In some cases the thyroid isthmus must then be retracted or clamped and divided, exposing the tracheal rings. A horizontal incision is made between the first and second rings, a tracheostomy tube is inserted into the airway, and placement is confirmed using standard methods.

Alternatively, and increasingly commonly, elective tracheotomy may be performed at the bedside by nonsurgical as well as surgical intensivists, using a percutaneous dilational technique. Numerous data are now available to suggest that this approach is equivalent to traditional tracheotomy in terms of safety and efficacy and, in fact, may be superior in many cases. Relative contraindications include coagulopathy and aberrant anatomy of the neck or trachea (e.g., morbid obesity or prior neck surgery).

Several percutaneous techniques have been developed over the past three decades, but none has been demonstrated to be superior. Common to all techniques is the creation of a small midline or transverse incision over the upper tracheal rings, puncture of the trachea at approximately the second ring with a needle, insertion of a guidewire into the airway, sequential dilation of the puncture site, and placement of a tracheostomy tube using a modified Seldinger technique. Use of bronchoscopic guidance is strongly recommended as this may reduce the incidence of posterior tracheal puncture, allows visual confirmation of tube placement, and facilitates periprocedure pulmonary toilet.

Troubleshooting Artificial Airways

COMPLICATIONS OF SURGICAL AIRWAYS

Early complications of cricothyrotomy and tracheotomy include periprocedure hemorrhage or aspiration, subcutaneous emphysema, unrecognized tracheal or esophageal injury, pneumothorax

or pneumomediastinum, and inadvertent decannulation. If accidental dislodgment of the tracheostomy tube occurs within the first 7 to 10 days, before the tract has matured, replacement of the tube risks creation of a false lumen. In this situation, orotracheal reintubation should be the first-line response. If appropriate personnel are at the bedside, the stoma can be quickly explored to assess patency and integrity of the tract. A #5 or #6 ET tube may be inserted through the stoma, or, alternatively, a suction catheter or bronchoscope may be placed in the airway as a guide for tube replacement.

Delayed complications of tracheotomy include wound infection, tracheal stenosis from the formation of granulation tissue, tracheomalacia leading to dynamic airway collapse, and tracheoarterial fistula. Tracheal stenosis and tracheomalacia have a peak incidence of ~6 weeks after decannulation. For the intensivist, preventing tracheal infection, minimizing tracheostomy tube diameter, avoiding mechanical irritation of the trachea by ensuring proper tracheostomy tube position, and maintaining cuff pressures no greater than 20 to 25 mm Hg (27-34 cm H_2O) are important factors in reducing the risk of subsequent tracheal stenosis and tracheomalacia (see Chapter 22 for more details related to tracheostomy management).

Tracheoarterial fistula is a rare but dreaded complication of tracheotomy that, as a rule, occurs at least 48 hours after tracheostomy placement. Although most cases involve the innominate artery, the left innominate vein, aortic arch, and right common carotid arteries have also been implicated. Classically described early warning signs include a small sentinel bleed and pulsation of the tracheostomy tube. Untreated, mortality from this complication is 100%, and even with prompt surgical intervention, 20% mortality has been reported. For this reason, any bleeding from a tracheostomy site must be investigated immediately. Active hemorrhage should be treated with the application of direct pressure using the tracheostomy tube or cuff or by inserting a gloved finger into the stoma and applying anterior pressure while preparations are made for immediate transport to the operating room.

APPROACH TO THE MALFUNCTIONING AIRWAY

Diagnosis and treatment of ventilator alarm situations are discussed in Chapter 47. However, loss of tidal volume or minute ventilation and sudden elevation in peak airway pressures can often be traced directly to the ET or tracheostomy tube. Except in situations where the patient is unable to tolerate even transient alveolar de-recruitment (e.g., patients with severe acute respiratory distress syndrome [ARDS]), airway troubleshooting should begin with disconnection from the ventilator and hand ventilation using a bag-valve mask. This step takes a number of potential sources of leak or other malfunction out of the equation and quickly establishes the adequacy of the airway.

Sudden elevations in peak pressure may be caused by coughing or Valsalva maneuvers, biting on the ET tube, kinking of the tube in the posterior oropharynx, or obstruction of the lumen by mucous or blood (Figure 30.E1). In the case of an ET tube, elevated airway pressures and oxygen desaturation may also reflect migration of the tube into a mainstem bronchus. After establishing the presence of bilateral breath sounds, the ET or tracheostomy tube should be suctioned to confirm tube patency and remove obstructive secretions. Instillation of saline may be helpful in this situation.

Loss of tidal volumes may be caused by a leaking or ruptured cuff or a faulty or disconnected pilot balloon. An ET tube that has been warmed and softened over time can sometimes develop a sigmoid curvature and herniate out of the glottic inlet, especially when more air is reflexively added to the pilot balloon to fix an apparent "leak."

Finally, high airway pressures may overcome the ability of the cuff to create an adequate seal, thereby causing loss of volume as air escapes around the cuff (see also Chapter 22). Flexible fiberoptic guidance can be invaluable in this situation. It is generally an unwise practice to keep increasing the pressure in the pilot balloon to seal the leak because of the increased risk of inducing tracheomalacia. It is better to diagnose and treat the cause of the increased airway pressures (Chapter 47).

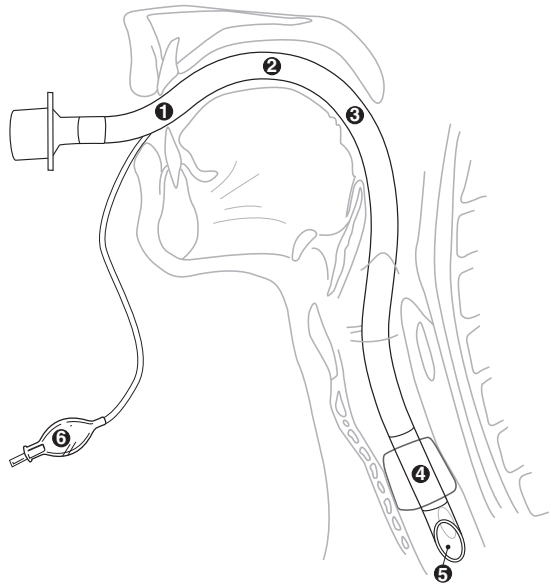


Figure 30.E1 Schematic representation of endotracheal tube inserted through the mouth into the trachea. Common problems with the tube arise at various points along its length, as designated by the numbers on the figure. *1,* Teeth (or gums) can occlude the tube (and tube can erode the corner of the mouth by pressure necrosis if not moved daily). *2,* Tongue can push the tube out. *3,* Tube can kink at the posterior pharynx. *4,* Cuff can deflate because of a leak or, if overinflated, can damage tracheal mucosa. *5,* Tip of tube (and its side opening) can be occluded by secretions or blood, or tip can be located too distally—that is, in the right main bronchus. *6,* Pilot balloon or its one-way valve can leak.

TUBE EXCHANGE

In the setting of cuff leak or intractable internal obstruction, the faulty tube will often have to be changed. Replacement of a mature tracheostomy tube generally requires no sedation and can be done by simply removing the old tube and inserting a new one or it may be done using a "railroad technique" over a soft suction catheter, analogous to the Seldinger's Method for vascular access (Chapter 22). An ET tube may be changed by elective extubation and rapid reintubation using direct laryngoscopy. However, after several days of mechanical ventilation, the airway architecture of most patients, even those who were easily intubated, will be altered by edema and inflammation. For this reason, many practitioners favor the use of a *tube exchange catheter*. These flexible catheters often incorporate a small lumen with multiple distal side holes and adapters to allow connection to a bag-valve mask or a jet ventilator. The tube exchanger is inserted into the ET or tracheostomy tube and functions as a guide and placeholder for the removal of the old tube and insertion of a new one over the exchanger. Some practitioners advocate concurrent laryngoscopy during tube exchange to visually confirm that the exchanger is in the airway and to facilitate repositioning of the new tube if it becomes snagged on the glottic inlet. In any case, it is important to remember that tube exchange should be approached with the same level of planning, precaution, and sedation used for initial intubations.

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Griffiths J, Barber VS, Morgan L, Young JD: Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation. BMJ 330(7502):1243, 2005 May 28. Epub 2005 May 18.

Although the number of studies were limited (five) and not combinable due to heterogeneity, the results of this meta-analysis suggested no difference in mortality but a potential shorter duration of mechanical ventilation and ICU length of stay for patients who had tracheostomies done earlier than later.

Hess DR: Tracheostomy tubes and related appliances. Respir Care 50:497-510, 2005.

This is a comprehensive and practical review by a internationally renowned respiratory care practitioner of the varieties of tracheostomy tubes and their usage in ICU and non-ICU patients.

Lavery GG, McCloskey BV: The difficult airway in adult critical care. Crit Care Med 36:2163-2173, 2008.

This reviews management of the difficult airway and other airway-related problems in ICU patients, including use of management algorithms.

Susarla SM, Peacock ZS, Alam HB: Percutaneous dilational tracheostomy: review of technique and evidence for its use. J Oral Maxillofacial Surgery 70:74-82, 2012.

This is an outstanding review and description of a technique that all intensivists should be familiar with.

CHAPTER 31

Alcohol Withdrawal: Diagnosis and Management

Amanda M. Ball ■ Barry D. Fuchs

Alcohol withdrawal syndrome (AWS) is a relatively common problem in the intensive care unit (ICU). However, the intensivist faces numerous challenges in accurately recognizing and appropriately treating this syndrome. First, the critically ill patient may not communicate to allow an accurate assessment of risk for AWS. In addition, because manifestations of AWS are nonspecific, the syndrome may be difficult to distinguish or may be obscured by concurrent medical conditions. Finally, the primary class of medications used to prevent or treat AWS, benzodiazepines, commonly cause or exacerbate delirium resulting from other medical conditions. Thus, one must maintain a high index of suspicion to recognize the patient at high risk for AWS and to accurately diagnose patients who develop the syndrome. This chapter provides an evidenced-based approach to the management of ICU patients who are at risk for, or who develop, AWS.

Alcohol Dependency and Alcohol Withdrawal Syndrome

Alcohol withdrawal syndrome (AWS) is defined by criteria listed in Box 31.1. Although overall mortality and morbidity due to AWS have steadily decreased with the advent of improved treatment and monitoring strategies, utilization of these strategies remains inconsistent. For instance, a considerable proportion (15% to 20%) of patients admitted to the hospital are alcohol dependent (as high as 39% in the ICU), yet studies show that only about half of these patients are initially identified as such by their physicians. Although this may in part be due to inaccurate self-reporting of true alcohol consumption, these data likely reflect lack of implementation of validated screening techniques for alcohol dependence. In addition, the decision process to give pharmacologic prophylaxis and the choice of which medication to use is not consistent or standardized. Although this is not widely appreciated, many patients who are alcohol dependent will *not* undergo alcohol withdrawal during hospitalization. In fact, only 5% to 7% of this patient population progress into AWS.

NEUROPHYSIOLOGY AND PHYSIOLOGY OF ALCOHOL WITHDRAWAL

Alcohol stimulates the brain's main inhibitory neurotransmitter, *gamma-aminobutyric acid* (GABA), by activating the $GABA_A$ receptor, which is responsible for the depressant effects of alcohol on the central nervous system (CNS). With chronic alcohol consumption, GABA receptors become less responsive to the same dosage of alcohol, which causes tolerance to develop. Alcohol also binds to and inhibits N-*methyl*-D-*aspartate* (NMDA) receptors in the brain, which inhibit the release of the excitatory neurotransmitter glutamate. Similar to the effects on GABA receptors, chronic exposure to alcohol causes up-regulation of NMDA receptors, which also contributes to the development of tolerance.

Additional online-only material indicated by icon.

BOX 31.1 ■ Criteria for Diagnosis of Alcohol Withdrawal Syndrome (AWS)

Patient manifests at least two of the following signs or symptoms that occur within hours to a few days following cessation of heavy and prolonged alcohol consumption and that cannot be attributed to another medical disorder:

1. Autonomic hyperactivity (e.g., sweating or heart rate > 100 beats per minute)
2. Tremors
3. Insomnia
4. Transient visual, tactile, or auditory hallucinations or illusions
5. Nausea or vomiting
6. Psychomotor agitation
7. Anxiety
8. Grand mal seizures

From Bayard M, McIntyre J, Hill KR, Woodside J Jr: Alcohol withdrawal syndrome. Am Fam Physician 69:1443-1450, 2004.

BOX 31.2 ■ Indication for Transfer to Intensive Care Unit (ICU) of Patients Diagnosed with Alcohol Withdrawal Syndrome (AWS)

1. If at any point during treatment patients cannot protect their airway, they should be intubated and transferred to the ICU for further management.
2. Patients with moderate alcohol withdrawal, defined as a CIWA-Ar* score of 9 to 15, who are deemed high risk for complications, including:
   a. the frail, older adult
   b. those with comorbidities including
      i. hemodynamic instability
      ii. pulmonary disease
      iii. pancreatitis
      iv. gastrointestinal bleeding
   c. those with an alcohol level > 100 mg/dL
   d. those who are unable to communicate (e.g., delirium) such that the CIWA-Ar cannot be used to guide treatment.
3. Patients with severe alcohol withdrawal syndrome, defined as the requirement for:
   a. > 6 mg of lorazepam (or equivalent) in the first hour, or
   b. ≥ 12 mg of lorazepam (or equivalent) in the first 6 hours, or
   c. CIWA-Ar that remains > 15 for > 1 hour with appropriate benzodiazepine treatment

**CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol (see Box 31.E2)*

Indication 3 is from Hack JB, Hoffman RS, Nelson LS: Resistant alcohol withdrawal: does an unexpectedly large sedative requirement identify these patients early? J Med Toxicol 2:55-60, 2006.

TIMING OF WITHDRAWAL SYMPTOMS

The manifestations of alcohol withdrawal range from mild tremors to seizures and death. The first signs and symptoms may begin within 6 to 36 hours from the time of the last alcoholic drink. The first signs of minor withdrawal often include mild anxiety, headaches, diaphoresis, gastrointestinal (GI) upset, and tremulousness (see Box 31.1). Alcohol withdrawal—related seizures, which occur in ~10% of patients, typically manifest as single or several brief generalized tonic-clonic seizures with short post-ictal periods within 6 to 48 hours after the last drink. Although status epilepticus may be caused by alcohol withdrawal, it is sufficiently rare that it

should prompt a search for an alternate etiology. Hallucinations, both visual and auditory, occur typically between 12 to 48 hours after the last alcoholic drink. In ~5% of patients, full delirium, agitation, extreme anxiety/fear, and progression to delirium tremens may occur 48 to 96 hours after the last drink. At this stage of withdrawal, patients may also exhibit vital sign instability, most notably tachycardia and hypertension. Although these time frames are general guidelines, in a given patient the timing and severity of withdrawal may vary significantly. Therefore, monitoring the progression of symptoms and signs is critical for making appropriate treatment decisions in individual patients.

DIAGNOSTIC SCREENING TOOLS

The diagnosis of AWS is clinical and based on the patient's history plus a high index of suspicion from the presenting signs and symptoms. However, standardized screening tools can be helpful for identifying patients at risk for alcohol-related disorders and hence for AWS. One commonly used tool is the 4-question CAGE questionnaire (Box 31.E1). Other well validated and rapid screening tools include the 3-question AUDIT (Alcohol Use Disorders Identification Test) (http://www.hepatitis.va.gov/provider/tools/audit-c.asp#S1X), the 10-question AUDIT (http://whqlibdoc.who.int/hq/2001/WHO_MSD_MSB_01.6a.pdf), and the NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test (NM ASSIST) (www.drugabuse.gov/nmassist/). The last is a convenient web-based interactive tool.

Once a patient at high-risk for alcohol withdrawal has been identified, the patient should be monitored closely for the development of signs and symptoms of AWS. The most widely studied and used scoring tool is the Revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar) (Box 31.E2). This 10-question assessment tool combines both patient responses to questions related to orientation, nervousness, and hallucinations and observations made by medical personnel to complete the score. In addition to being a tool to monitor the emergence of AWS, because the CIWA-Ar score tracks the severity of the withdrawal (see Box 31.E2), it is also used to guide the titration of medicines used to treat AWS. Although the CIWA-Ar quantifies the clinical manifestations of AWS, these are *not* specific to alcohol withdrawal. As such, other states of withdrawal and other medical conditions associated with an increase in catecholamines may mimic or coexist with AWS and cause a false-positive increase in the CIWA-Ar score (e.g., delirium, meningitis, drug ingestions, liver failure). Therefore, before initiating medical treatment for AWS, based on an elevated CIWA-Ar score, it is essential to assess the patient first to rule out other potential causes.

Importantly, one should not use the CIWA-Ar in a noncommunicative patient (e.g., one who is delirious or intubated). Regrettably, there is no standard assessment tool for monitoring such patients; however, in these cases it is reasonable to use a validated ICU sedation agitation scale to quantify the severity of agitation (e.g., the Richmond Agitation-Sedation Scale [RASS] [see Table 5.2, Chapter 5]). Similar to the CIWA-Ar, an increased RASS score is not specific for alcohol withdrawal; however, it is useful to guide therapeutic management. For example, clinicians can target treatment with benzodiazepines to a RASS goal of −2 to +1 to have objective drug administration goals.

INDICATIONS FOR TRANSFER TO THE ICU

Once one diagnoses AWS (Box 31.1), one must consider whether the patient has indications for ICU level of care (see Box 31.2). Patients who don't meet the criteria in Box 31.2 for admission to the ICU should be able to be managed on a general medical floor—provided that the floor unit's nursing staff has been trained to perform CIWA-Ar scoring in conjunction with a protocolized or physician-driven titration of appropriately dosed benzodiazepines.

BOX 31.E1 ■ CAGE Questionnaire to Screen for Alcohol Use Disorder

CAGE Questions*

1 Have you ever felt you needed to **C**ut down on your drinking?
2 Have people **A**nnoyed you by criticizing your drinking?
3 Have you ever felt **G**uilty about drinking?
4 Have you ever felt you needed a drink in the morning (**E**ye-opener) to steady your nerves or get rid of a hangover?

**Two or more positive answers is considered as a positive screen.*

From Liskow B, Campbell J, Nickel EJ, Powell BJ: Validity of the CAGE questionnaire in screening for alcohol dependence in a walk-in (triage) clinic. J Stud Alcohol 56:277-281, 1995.

BOX 31.E2 ■ Clinical Institute Withdrawal Assessment for Alcohol: CIWA-Ar*

Date/Time

Rater's Initials/Signature

1. Nausea and Vomiting—"Do you feel sick to your stomach? Have you vomited?"

OBSERVATION.

0 No nausea and no vomiting
1 Mild nausea with no vomiting
4 Intermittent nausea with dry heaves
7 Constant nausea, frequent dry heaves and vomiting

2. Tremor—Arms extended and fingers spread apart

OBSERVATION.

0 No tremor
1 Not visible, but can be felt fingertip to fingertip
4 Moderate, with patient's arms extended
7 Severe, even with arms not extended

3. Paroxysmal Sweats

OBSERVATION.

0 No sweat visible
1 Barely perceptible sweating, palms moist
4 Beads of sweat obvious on forehead
7 Drenching sweats

4. Anxiety—"Do you feel nervous?"

OBSERVATION.

0 No anxiety, at ease
1 Mildly anxious
4 Moderately anxious, or guarded, so anxiety is inferred
7 Equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions

5. Agitation

OBSERVATION.

0 Normal activity
1 Somewhat more than normal activity
4 Moderately fidgety and restless
7 Paces back and forth during most of the interview, or constantly thrashes about

Continued on following page

BOX 31.E2 ■ Clinical Institute Withdrawal Assessment for Alcohol: CIWA-Ar* (Continued)

6. Tactile Disturbances—"Have you any itching, pins and needles sensations, any burning, any numbness or do you feel bugs crawling on or under your skin?"

OBSERVATION.
0 None
1 Very mild itching, pins and needles, burning or numbness
2 Mild itching, pins and needles, burning or numbness
3 Moderate itching, pins and needles, burning or numbness
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

7. Auditory Disturbances—"Are you more aware of sounds around you? Are they harsh? Are you hearing things that you know are not there?"

OBSERVATION.
0 Not present
1 Very mild harshness or ability to frighten
2 Mild harshness or ability to frighten
3 Moderate harshness or ability to frighten
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

8. Visual Disturbances—"Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things that you know are not there?"

OBSERVATION.
0 Not present
1 Very mild sensitivity
2 Mild sensitivity
3 Moderate sensitivity
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

9. Headache, Fullness in Head—"Does your head feel different? Does it feel like there's a band around your head?" Do not rate for dizziness or lightheadedness.

OBSERVATION.
0 Not present
1 Very mild
2 Mild
3 Moderate
4 Moderately severe
5 Severe
6 Very severe
7 Extremely severe

BOX 31.E2 ■ Clinical Institute Withdrawal Assessment for Alcohol: CIWA-Ar* (Continued)

10. Orientation and Clouding of Sensorium—"What day is this? Where are you? Who am I?"

OBSERVATION.

0 Oriented and can do serial additions
1 Cannot do serial additions or is uncertain about the date
2 Disoriented for date by no more than 2 calendar days
3 Disoriented for date by more than 2 calendar days
4 Disoriented for place and/or person

Sum of the scores for Questions 1-10 equals CIWA-Ar Score*

For dose of lorazepam to be administered based on CIWA-Ar Score , see Figure 31.E1. For triage to ICU or not based on CIWA-Ar Score, see Box 31.2.

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*Scoring: 0–8, mild withdrawal; 9–15, moderate withdrawal; > 15, severe withdrawal (Shaw JM, Kolesar GS, Sellers EM et al: Development of optimal treatment tactics for alcohol withdrawal. I. Assessment and effectiveness of supportive care. J Clin Psychopharmacol 1:381-388, 1981).

From Sullivan JT, Sykora K, Schneiderman J, et al: Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict 84:1353-1357, 1989.

BOX 31.3 ■ Recommended Lorazepam Prophylaxis of Alcohol Withdrawal Syndrome (AWS)

First Day: 1 or 2 mg by mouth (or naso-gastric tube) every 6 hours for 4 doses
Second and Third Days: 1 mg by mouth (or naso-gastric tube) every 6 hours for 8 doses and then reassess

Note: If symptoms of AWS are noted, either initiate AWS treatment based on symptom severity or increase the dose or frequency of the prophylaxis regimen and slow the taper schedule.

Adapted from Mayo-Smith MF for the American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. Pharmacologic management of alcohol withdrawal: a meta-analysis and evidence-based practice guideline. JAMA 278:144-151, 1997.

Treatment

INITIAL MANAGEMENT

The initial treatment of a patient with suspected or diagnosed AWS includes several supportive care measures. Patients should be assessed for the ability to protect their airway and the need for mechanical ventilation. Because these patients are often volume depleted on presentation, circulatory support with infusions of either normal saline or lactated Ringer's solution is usually required to restore and maintain organ perfusion.

In addition, because these patients often suffer from severe nutritional deficiencies resulting from poor dietary intake, they should all receive thiamine, folic acid, and multivitamin supplementation. Importantly, thiamine 100 mg, intravenously (IV) (or orally), should be given as soon as possible, prior to the administration of any glucose-containing fluid to avoid precipitating Wernicke's encephalopathy. Thiamine is a cofactor for the Krebs cycle enzymes alpha-ketoglutarate dehydrogenase and pyruvate dehydrogenase and is utilized during the metabolism of carbohydrate. If the patient is thiamine deficient, as is often seen in patients with alcohol dependence, these enzymes will not function normally, which may impair adenosine triphosphate (ATP) synthesis and lead to neuronal cell death. To fully replete vitamin stores, patients should receive at least 3 to 5 days of repletion. When feeding is resumed either by mouth, total enteral nutrition, or total parenteral nutrition, one should monitor closely for the refeeding syndrome (Chapter 15). Given all these considerations, one should consult with a clinical nutritionist early on to assist with the management of these deficiencies.

Patients with AWS should have several laboratory parameters evaluated initially including a basic metabolic panel (serum glucose, electrolytes, BUN and creatinine), and serum calcium, magnesium, and phosphorus. If the anion gap is elevated (see Equation 4, Chapter 83), a serum osmolarity should also be obtained to calculate the osmolar gap (see Equation 5, Chapter 83) to screen for co-ingestions such as methanol or ethylene glycol (Chapter 57). In addition, one should obtain a urine drug screen and a urine analysis, serum ethanol level, prothrombin time, liver function tests, and serum levels for amylase, lipase, creatinine phosphokinase, lactic acid, and albumin. Patients with AWS should have daily serum chemistry and electrolyte panels, especially as nutrition is initiated. Most important, phosphorus may decrease dramatically and may require daily standing repletion to avoid severe complications (Chapter 15).

BENZODIAZEPINE PROPHYLAXIS

Patients with alcohol dependence who are admitted for an unrelated medical or surgical problem are at risk for developing AWS, which may complicate medical or surgical management. Thus, all

patients should be screened systematically for alcohol dependence so that this complication can be anticipated and appropriately managed. Nurses or physicians can perform the initial screening using the CAGE or other tools (see Box 31.E1). However, if nurses routinely screen patients, a positive screen should always prompt notification of the physician. The physician should then confirm that the patient is at high risk for AWS and decide on the appropriate management. All such patients should at least be monitored closely by nursing staff for the development of early signs of AWS using the CIWA-Ar scale (see Box 31.E2).

If a patient admitted for elective surgery is identified to be at high risk for AWS, it may be prudent to cancel surgery or delay surgery while instituting AWS prophylaxis to get the patient through the withdrawal. Given the absence of an active concurrent medical or surgical problem, initiating prophylaxis with lorazepam is unlikely to confound or exacerbate the patient's condition. In these cases, the onset of agitation or delirium in such patients is highly likely to be AWS.

In contrast, routine AWS prophylaxis in nonelective surgery patients or medical patients is not recommended, as it may complicate the underlying medical or surgical condition. One exception, wherein prophylaxis should be considered, is if the patient is at high risk for delirium tremens (DTs) or withdrawal seizures, based on a prior history of having had one of these complications. DTs, an acute and sometimes fatal complication of abrupt withdrawal of excessive alcohol intake, is characterized by agitation, hallucinations, disorientation, confusion, fear, and anxiety. Patients can also exhibit tachycardia, diaphoresis, tremors, and gastrointestinal (GI) distress.

However, even in these cases, the primary physician should only initiate benzodiazepine prophylaxis after careful assessment. (See Box 31.3 for one recommended medical regimen for prophylaxis.) In all others, close monitoring for AWS using the CIWA-Ar remains useful since this ensures appropriate and timely treatment should AWS occur.

SYMPTOM-TRIGGERED VERSUS FIXED-SCHEDULE TREATMENT APPROACH

There are two different strategies for the medical management of patients undergoing AWS: symptom-triggered (recommended) or fixed-schedule approaches. With the symptom-triggered approach, the patient is monitored with the CIWA-Ar scale (or RASS for intubated patients) to first assess the severity of the withdrawal symptoms to justify the need for medical treatment.

The alternative, fixed-schedule therapy, also called the front-loading approach, prescribes scheduled benzodiazepine treatment proactively to patients whom prescribers anticipate may progress into moderate to severe AWS. Although a potential advantage of this approach is that it may blunt or minimize the appearance of signs of severe AWS when compared to a symptom-triggered protocol, the fixed-schedule approach has been associated with excessive benzodiazepine use in patients with moderate AWS. Fixed-schedule treatment is also associated with more prolonged hospitalizations and duration of ICU stays. Excessive benzodiazepine use may lead to even more serious problems than the AW itself (e.g., aspiration, falls, and respiratory failure). Another benefit of the symptom-triggered approach is that it provides the ability to identify the specific signs and symptoms of withdrawal and to monitor their severity and resolution over time.

BENZODIAZEPINE SELECTION

Based on historical and now evidence-based literature, benzodiazepines are the mainstay of treatment for alcohol withdrawal. Seven benzodiazepines are available in the United States: lorazepam (Ativan), midazolam (Versed), diazepam (Valium), oxazepam (Serax), alprazolam (Xanax), chlordiazepoxide (Librium), and temazepam (Restoril). Of these, alprazolam, midazolam, and temazepam have the least clinical use and evidence base for the treatment of AWS and will not be discussed further.

Oxazepam is not an optimal agent for AWS for several reasons. First, it has a short half-life of 2.8 to 8.6 hours and often requires dosing every 6 hours to prevent symptom breakthrough. Oxazepam is only available in an oral capsule formulation, which is unsuitable for the management of severe AWS or AWS in ICU patients with only intravenous (IV) access available. Oxazepam also has the least evidence to support its use in the treatment of AWS.

The remaining three agents (lorazepam, diazepam and chlordiazepoxide) at equivalent dosages and with appropriate monitoring are considered equally efficacious in the treatment of AWS. Choice among these 3 agents should be based on institutional preference, patient factors (weight, hepatic function, renal function, and age), and drug availability.

Early, adequate, and appropriately escalated drug dosing of benzodiazepines in the treatment of AWS is critical to prevent progression to more severe AWS or DTs. AWS patients usually require higher doses than prescribers often initially anticipate because of up-regulation of GABA receptors from chronic alcohol consumption. During severe AWS and DTs, patients may require dosages up to 20 to 25 mg of IV lorazepam and 100 to 150 mg IV diazepam in single boluses. These doses can be given safely often without requiring intubation under the appropriate clinical and monitoring circumstances.

ADJUVANT AGENTS

Severe withdrawal is frequently associated with adrenergic hyperactivity symptoms, agitation, and DTs. As a general rule, if these findings are prominent—in the absence of other features of AWS—one should suspect an alternative etiology and evaluate appropriately. However, a number of adjuvant agents could be used in conjunction with benzodiazepines, where appropriate, for AWS treatment. Examples include clonidine, carbamazepine, valproic acid, and haloperidol. Each agent is used for specific symptoms during AWS with variable levels of evidence of support.

Clonidine is utilized for the adrenergic hyperactivity that patients may often exhibit during the later stages of AWS. Clonidine is an alpha-2 adrenoreceptor agonist primarily prescribed for patients with hypertension but also has effects within the medulla oblongata to decrease sympathetic tone for the treatment of withdrawal states. If the patient has cardiovascular comorbidities, it is often prudent to treat the patient's signs and symptoms of adrenergic hyperactivity (e.g., systolic blood pressure [SBP] > 140 mm Hg, diastolic blood pressure [DBP] > 90 mm Hg, heart rate [HR] > 100/min) with clonidine in addition to lorazepam.

Suggested order for clonidine dosing is as follows:

Clonidine: 0.1 mg orally (PO) every 1 hour (q1h) as needed (PRN) for SBP > 160 mm Hg or DBP > 100 mm Hg. Repeat for up to three doses. Contact prescriber if further doses are required to maintain blood pressure (BP). Alternatively, doses may be scheduled: 0.1 mg PO every 6 to 8 hours (Q6h to Q8h).

Carbamazepine (CBZ) (Tegretol) can be considered in mild and moderate AWS to prevent "kindling" and progression to more severe AWS. However, the majority of the data with CBZ is in alcohol withdrawal rehabilitation centers as opposed to inpatient acute care hospitals or ICUs. There are only a few studies evaluating CBZ in acute AWS—all with small sample sizes. CBZ may have more utility in the long-term management of alcohol withdrawal, as the pilot data available have longer follow-up (4 months) and typically occur in outpatient treatment centers. The mechanism of action of CBZ is not fully elucidated but interaction with GABA receptors may be partially responsible for its effectiveness during both treatment and prevention of AWS.

A proposed dosing strategy for CBZ is as following:

Carbamazepine: 200 mg PO four times daily (QID) for days 1 to 3, taper to 200 mg PO times daily (TID) for days 4 to 7, 200 mg PO twice a day (BID) for day 8, then 200 mg for day 9 and then off.

Valproic acid has a similar proposed mechanism of benefit in the treatment and prevention of AWS as CBZ. Although a number of studies evaluated valproic acid in AWS, limitations in their study design, small sample sizes, heterogeneity in criteria used to diagnose AWS and in comparator treatments, and concerns about their generalizability have prevented widespread acceptance and use of valproic acid in AWS. It is not currently recommended because of lack of data.

If utilized, the following is a proposed dosing strategy for valproic acid:

Valproic acid: 500 mg every 8 hours for 7 days, then discontinue without a taper.

For DTs and severe agitation, in addition to benzodiazepines, the preferred agent to add is *haloperidol*. Before initiating haloperidol, a baseline electrocardiogram (ECG) should be obtained to ensure the patient's QTc is < 450 msec (and deficits in potassium/magnesium/calcium should be corrected). After treatment begins, daily ECGs should be performed, and if the QTc prolongs to > 500 msec, haloperidol should be discontinued. Haloperidol may lower the seizure threshold and therefore should be used with caution in those with a known seizure disorder or history of alcohol withdrawal seizures.

The following is a proposed dosing strategy for haloperidol usage for delirium tremens or severe agitation:

Haloperidol: 5 to 10 mg IV/IM q1 to 2 hours PRN for agitated delirium or 2.5 to 5 mg PO q1 to 2 hours PRN. The maximum total dose of haloperidol should be 40 mg per day to decrease the risk of torsades de pointes (Chapter 34.)

RESISTANT ALCOHOL WITHDRAWAL (RAW) TREATMENT

A small subset of patients who progress to severe AWS may develop resistant alcohol withdrawal (RAW). Although there is no standard definition of RAW, one proposed definition is described in Box 31.4.

Once a patient demonstrates a requirement for higher dosages of benzodiazepines to control or maintain symptoms, other agents may be considered for RAW. One agent that has been studied in ICU patients for RAW is *phenobarbital*. Phenobarbital is also active at the GABA receptor and may augment the efficacy of benzodiazepines at the $GABA_A$ receptor. One such study by Gold et al, using a before-after design, integrated the use of phenobarbital with escalating, high doses of benzodiazepines based on the patient's response using the Riker sedation scale. Patients received three doses of phenobarbital, 65 mg IV over 30 minutes, once patients required 40 mg IV diazepam as a single dose (equivalent to 8 mg IV lorazepam). The addition of phenobarbital along with an aggressive diazepam symptom-based dosing strategy reduced the need for mechanical ventilation from 47% to 22% (P = 0.008). This occurred despite increasing both maximal individual dosage of diazepam (32 mg versus 86 mg, P = 0.01) and total amount of diazepam utilized (248 mg versus 562 mg, P = 0.01).

BOX 31.4 ■ Proposed Definition of Resistant Alcohol Withdrawal (RAW)

Lack of satisfactory control of manifestations of alcohol withdrawal syndrome (AWS) after intravenous (IV) treatment of:

1. Lorazepam 40 mg (or equivalent dosage of another benzodiazepine) in 3 hours OR
2. Lorazepam 80 mg (or equivalent dosage of another benzodiazepine) in 8 hours OR
3. Lorazepam dose ≥ 8 mg/single dose for control (or equivalent dosage of another benzodiazepine)

From Hack JB, Hoffman RS, Nelson LS: Resistant alcohol withdrawal: Does an unexpectedly large sedative requirement identify these patients early? *J Med Toxicol* 2:55-60, 2006.

Propofol, another agent that is active at the GABA receptor, has been utilized to treat RAW. Its use in alcohol withdrawal has been limited mostly to severe AWS or refractory AWS unresponsive to treatment with benzodiazepines and barbiturates. There are both case reports and case series describing successful use of propofol infusion for RAW. In these cases, propofol was initiated after extremely high doses of lorazepam were utilized (> 1000 mg) with duration of propofol use ranging from 4 to 11 days. Importantly, if a propofol infusion is used for > 48 hours, triglycerides and creatinine phosphokinase should be assessed every 48 hours (Chapter 5). Likewise, the lipid component of propofol must also be factored in to the total nutritional intake for the patient (1.1 kcal/mL). Finally, adhering to the recommended maximum dose for propofol of 80 mcg/kg/min is critical for patient safety, as exceeding this limit has been associated with the rare, but highly fatal, propofol infusion syndrome (Chapter 57).

Dexmedetomidine, one of the newer agents available and approved by the Food and Drug Administration (FDA) for ICU sedation management, has also been utilized for AWS. Dexmedetomidine, similar to clonidine, is a selective central alpha-2 adrenoreceptor agonist with sedative and anxiolytic properties. Only a few case reports utilized dexmedetomidine in patients with AWS. In each of the cases described, the patients still received benzodiazepines (diazepam bolus or midazolam infusion) and haloperidol as needed. Dexmedetomidine was discontinued within 24 hours of discontinuation of benzodiazepines and haloperidol. The doses of dexmedetomidine were titrated from 0.2 mcg/kg/h up to 0.7 mcg/kg/h as a maintenance infusion. The role of dexmedetomidine in AWS remains unclear, as the level of evidence is still low at case reports only, desired dosing is unclear, and benzodiazepines are still required for treatment.

PROTOCOLIZED MANAGEMENT OF AWS IN THE ICU

Just as utilizing a systematic, standardized process for identifying high-risk patients for alcohol dependence and AWS improves identification over physician-dependent screening alone, many argue that a protocolized approach to the treatment of AWS in ICU patients is preferred compared to a nonuniform approach. One such ICU management algorithm is presented online for convenient web access and utilization (see Figure 31.E1).

An annotated bibliography can be found at www.expertconsult.com.

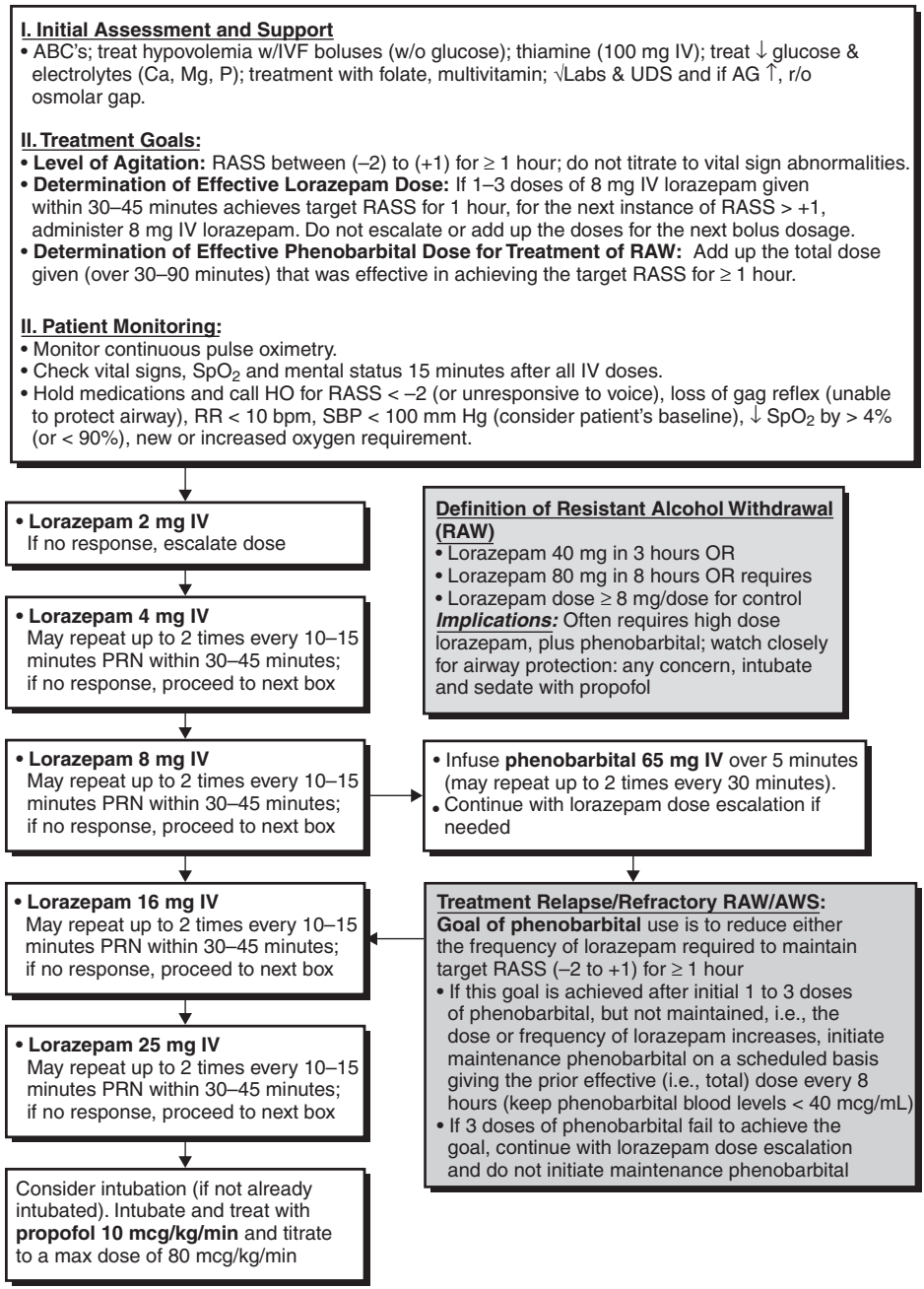


Figure 31.E1 Alcohol withdrawal treatment algorithm for patients in intensive care units. ABC's, Airway, Breathing, Circulation; AG ↑, increased anion gap (see Chapter 83); AWS, alcohol withdrawal syndrome; bpm, breaths per minute; Ca, calcium; CPK, creatinine phosphokinase; HO, house officer (resident physician); IV, intravenous; IVF, intravenous fluid (crystalloid); Labs, laboratory tests (complete blood count with differential cell count, basic metabolic panel or panel 7 [serum sodium, chloride, potassium, bicarbonate, BUN, creatinine and glucose]); max, maximum; Mg, magnesium; P, phosphate; PRN, as needed; RASS, Richmond agitation-sedation scale (see Chapter 5); RAW, resistant alcohol withdrawal; r/o, rule out; RR, respiratory rate; SBP, systolic blood pressure; SpO_2, oxygen saturation measured by pulse oximetry; UDS, urine drug screen; w/, with; w/o, without; ↓ glucose, decreased blood glucose concentration; ✓, check. *(Provided by Amanda M. Ball, Pharm. D., and Barry Fuchs, M.D., of the Hospital of the University of Pennsylvania.)*

Continued

Weaning Medications:

- **Lorazepam:** Once goal lorazepam dose achieved, continue PRN dosing for 24 hours. After 24 hours, reassess patient and consider initiation of taper/weaning of lorazepam dosage based on RASS (consult with pharmacy). Transition to oral PRN.
- **Phenobarbital:** Taper by 50% every 2–3 days.
- **Propofol:** √Triglycerides and CPK every 48 hours while on propofol. Perform daily interruption of sedation after 24 hours of continuous use and assess continued need for propofol, instead of lorazepam, for severe alcohol withdrawal. If patient tolerates propofol interruption with RASS ≤ 1, resume lorazepam dosing PRN based on RASS at lower dosage than previously used (consult with pharmacy for specific dosing recommendations).

Figure 31.E1, cont'd

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Stanley KM, Worrall CL, Lunsford SL, et al: Experience with an adult alcohol withdrawal syndrome practice guideline in internal medicine patients. Pharmacotherapy 25:1073-1083, 2005.

This study used a before-after design and found that use of AWS monitoring and symptom-based treatment protocol using adjunctive medications resulted in better outcomes than their baseline control group managed with benzodiazepines exclusively.

CHAPTER 32

Allergies to Antibiotics

Patricia Takach

Adverse drug reactions (ADRs) are responsible for 2% to 5% of hospitalizations in the United States. In addition, an estimated 30% of patients experience an ADR during their hospitalization. Allergic reactions account for 5% to 10% of these ADRs, and 1 of every 25 to 50 of these reactions is severe and life threatening. There are reports of increased frequency of ADRs in the intensive care unit (ICU) compared to that in non-ICU areas. In the United States, 1 in 300 hospitalized patients die from ADRs (~100,000 annually with 6% to 10% potentially allergic in origin).

Drug reactions are classified into two major groups: predictable (type A, from known pharmacologic properties, can occur in anyone) and unpredictable (type B, uncommon, restricted to a vulnerable subpopulation) (Figure 32.1). Unpredictable reactions include drug allergy (immunologic), pseudoallergic reactions, drug intolerance, and idiosyncratic reactions. Serious outcomes can be associated with immediate hypersensitivity allergic reactions known as a type I reaction, based on the four traditional types of immunologic reactions of the Gell and Coombs classification system (Table 32.1). This chapter focuses on the evaluation and prevention of potentially life-threatening immediate hypersensitivity reactions to antibiotics.

Evaluations of Patients with a History of Antibiotic Allergy

Beta-lactam antibiotics are among the most important causes of allergic reactions. This group includes penicillin and its semisynthetic chemical derivatives (such as ampicillin and amoxicillin) and other beta-lactam antibiotics including cephalosporins, carbapenems, and monobactams. Approximately 10% of patients report a history of penicillin allergy; however, up to 90% of these patients may be able to tolerate penicillin after a complete evaluation (Figure 32.1). A carefully obtained history of previous drug reactions to this class of antibiotics is critical to the allergy evaluation. An accurate history may be challenging in the ICU setting where patients are frequently sedated or intubated and may be receiving multiple medications. Family members or the patient's primary care physician as well as outpatient electronic medical records may be valuable sources of the relevant history. Inquiry should be obtained for the name of the drug, time when previous exposure occurred, reason for treatment, timing of previous reaction (time elapsed from drug administration to the occurrence of adverse events), characteristics of the reaction (organ systems involved), medications in use at the time of the reaction, management required for treatment of the reaction, subsequent exposure to the drug, similar symptoms in absence of the drug (such as chronic urticaria), and whether the patient had an underlying condition that favored a reaction to a medication. For example, patients with Epstein Barr virus infections who are given ampicillin tend to develop a rash that looks like an allergic reaction but is not immunologically mediated. Information is then collected regarding all the current medications, both prescription and nonprescription, and similarly reviewed. Physical examination and laboratory studies to assess for organ system involvement are also crucial to the evaluation.

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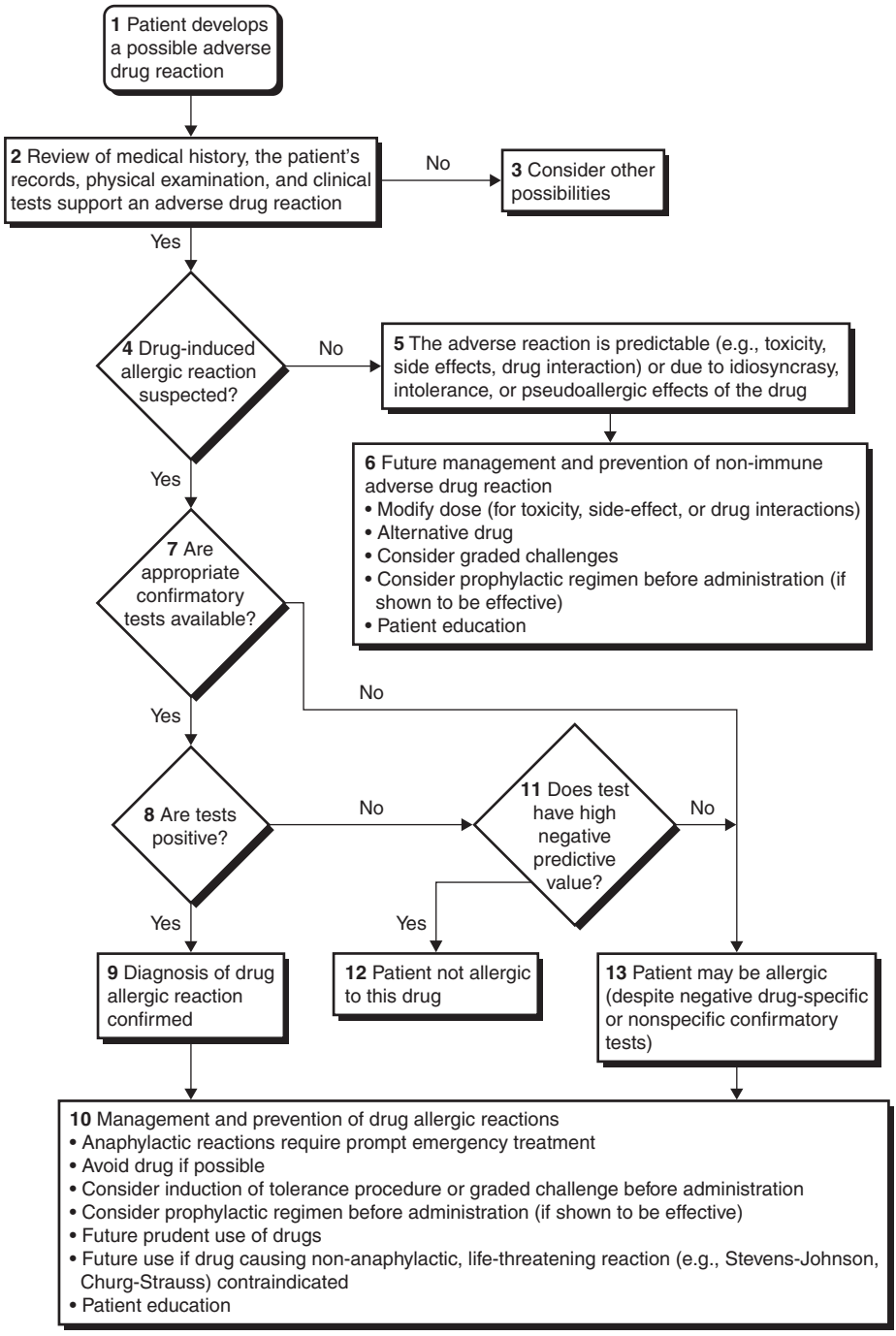


Figure 32.1 Approach to a patient with a possible adverse drug reaction, including allergic drug reactions. *(Adapted from Drug Allergy: Updated Practice Parameters 2010, Rolensky and Khan [eds]. Ann Allergy 105:273e1-273e78, 2010.)*

TABLE 32.1 ■ **Classification of Allergic Reactions (Gell and Coombs)**

Type	Description	Mechanism	Clinical Features
I Immediate reaction (30–60 min) Accelerated reaction (1–72 hours)	Immediate hypersensitivity	IgE-mediated degranulation of mast cells and basophils	Anaphylaxis Angioedema Bronchospasm Urticaria (hives)
II	Antibody-mediated cytotoxicity	Antigen binds to cell; IgG or IgM combines with antigen and with complement to destroy cell	Hemolytic anemia Interstitial nephritis
III	Immune complex disease	Antigen and IgG or IgM form complexes that deposit in tissue, fix complement, and cause local inflammation and injury	Serum sickness
IV	Delayed hypersensitivity	Lymphocyte-mediated	Contact dermatitis
V (> 72 hours)	Idiopathic	Uncertain	Maculopapular rash Stevens-Johnson syndrome (exfoliative dermatitis)

IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M.
Modified from Weiss ME, Adkinson NF: Immediate hypersensitivity reactions to penicillin and related antibiotics. Clin Allergy 18:515-540, 1988.

Allergic drug reactions may be classified according to the temporal relationship of onset of symptoms that include immediate (minutes to an hour), accelerated (an hour to 3 days), and delayed (beyond 3 days). If the initial reaction is immediate (i.e., occurring within 30 to 60 minutes of the drug administration), the patient is considered to be at high risk for a potentially life-threatening immediate hypersensitivity reaction such as anaphylaxis. *Anaphylaxis* is an immediate, immunologically mediated, systemic reaction to antigen and is characterized by smooth muscle contraction and capillary dilatation resulting from the release of mediators from mast cells and basophils.

The time interval since the previous ADR is also significant: ADRs occurring within the last year are more likely to recur on challenge with the antibiotic than are reactions that took place more than 10 years in the past. Patients are at intermediate risk for a life-threatening allergic reaction if they have only a remote (> 10 years prior) history of anaphylaxis.

Skin Testing for Beta-Lactam Antibiotics

Skin testing is the most reliable method of determining if the patient with a prior allergic history to beta-lactam antibiotics is truly at risk for an immediate hypersensitivity reaction to penicillin or other beta-lactam antibiotics. This procedure is performed using reagents containing the major antigenic determinant and penicillin G. The major determinant, benzylpenicilloyl poly-L-lysine (PPL), is available commercially as Pre-Pen. Approximately 95% of penicillin is converted in the body to the major antigenic determinant, and the remainder includes the minor antigenic determinants. Minor determinants mixture (MDM) of penicillin is not commercially available in the United States at this time. Penicillin challenges, however, of subjects with negative skin test responses to PPL and penicillin G have similar reaction rates compared with those in subjects

with negative skin test responses to the full set of major and minor penicillin determinants. A less common antigen includes the R-group side chain found on beta-lactams. An example would be a selective allergy to amoxicillin but tolerance of other penicillins. Antihistamines must be avoided for 1 week prior to skin testing. Approximately 10% of patients with a history of a previous allergic reaction to penicillin have positive skin test results to the drug. Patients with a positive skin test result detect penicillin-specific IgE antibody with a wheal and flare reaction to the major determinant or penicillin G compared to the control reagents. If testing is positive, then treatment with desensitization or "induction of tolerance" is required.

Predictive Value of Skin Testing

The *negative predictive value* of a negative skin test to both major and minor determinants, representing the percent of patients with negative skin test results who will tolerate beta-lactam therapy without an immediate allergic reaction, is 97%, with 1% to 3% of patients with negative skin test responses (with both major and minor determinants) experiencing mild and self-limiting reactions on being challenged with the drug.

In addition, patients with negative skin tests who do react on challenge with a penicillin tend to have mild reactions. However, negative penicillin skin test results have no predictive value for the development of non-IgE-mediated reactions such as serum sickness, Stevens-Johnson syndrome, hemolytic anemia, maculopapular rashes, drug fever, or interstitial nephritis. Patients may also experience urticarial eruptions late in the course of therapy despite an initial negative skin test result.

The positive predictive value of the penicillin skin test (i.e., the number of patients with positive skin tests who will experience anaphylactic reactions on receiving beta-lactam antibiotics) is between 40% and 100%.

Indications for Skin Testing

Skin tests are indicated for any patient with a history of penicillin allergy who requires a beta-lactam drug to treat *a life-threatening condition* when *no other alternative antibiotic is appropriate*. Skin tests should be avoided in those patients at *high risk* for an anaphylactic reaction as determined by history. These patients should be desensitized to penicillin if the drug must be given. Contraindications to skin testing include the lack of a suitable site to perform the test (e.g., secondary to rash), the use of antihistamines, the presence of dermatographism (may cause false-positive reaction), or inadequate skin test controls.

Skin test results to penicillin may remain negative up to 6 weeks after an allergic reaction to beta-lactam antibiotics. Skin testing should, therefore, be repeated after this interval if it is initially negative and the test is clinically indicated. A history of penicillin-induced exfoliative dermatitis (i.e., Stevens-Johnson syndrome or toxic epidermal necrolysis [see Chapter 43]) is *an absolute contraindication* to skin testing as well as to the administration of beta-lactam antibiotics. The approach to a patient with a history of a beta-lactam allergy is summarized in Figure 32.1.

Although most investigators feel that penicillin skin tests are predictive of reactions to other semi-synthetic penicillins, controversy does exist. It is recommended that patients who have a history of a recent and severe reaction to a semisynthetic penicillin (i.e., they are at high risk for an anaphylactic reaction) continue to avoid the specific antibiotic that caused the reaction, even if penicillin skin test results are negative.

The risk of having an adverse reaction to the skin test reagents is less than 1%, but systemic and fatal reactions occur. The risk of becoming sensitized to beta-lactam antibiotics as a result of penicillin skin testing is also less than 1%. Resensitization after oral treatment with penicillin is

rare, and repeat skin testing is not required in patients who have tolerated 1 or more oral courses of penicillin. Resensitization after high-dose parental penicillin may be more likely. Retesting may be considered in individuals with recent or particularly severe previous reactions.

Evaluation of Allergies to Cephalosporins and Other Non–Beta-Lactam Antibiotics

Patients with a positive penicillin skin test response to penicillin have a slightly increased risk (~2%) of reacting to cephalosporins, and some of these reactions may be anaphylactic reactions. A group of studies evaluated patients with positive penicillin skin tests (PPL, penicillin G, or MDM) who were challenged with cephalosporins. The overall reaction rate was 3.4%; if the analysis was limited to studies published after 1980 when cephalosporins were no longer contaminated with penicillin, the reaction rate was reduced to 2%.

Therefore, depending on the reaction history, these patients should be administered cephalosporin through graded challenge or desensitization (induction of tolerance procedure). If a patient has a history of a cephalosporin allergy but a negative penicillin skin test result, one should consider a penicillin, *not* a cephalosporin (Figure 32.E1).

Allergic cross-reactivity between shared R-group side chains should also be considered. Amoxicillin and certain cephalosporins share identical R-group side chains (see Tables 32.E1 and 32.E2). Research has shown that 12% to 38% of patients proved to be selectively allergic to amoxicillin reacted to cefadroxil yet were able to receive penicillin. Therefore, patients with an amoxicillin or an ampicillin allergy should avoid cephalosporins that share identical R-group side chains or undergo desensitization of these cephalosporins.

No clinically significant cross-reactivity among the monobactam, *aztreonam*, and penicillin has been demonstrated. Thus, patients with positive skin test to penicillin can be given this drug safely. However, aztreonam has been known to cross-react with ceftazidime, so patients allergic to either antibiotic should avoid both. The current Joint Task Force on Drug Allergy: Updated Practice Parameters 2010 report limited data indicating a lack of significant allergic cross-reactivity between penicillin and carbapenems. These parameters noted that penicillin skin test–negative patients may receive carbapenems, whereas penicillin skin test–positive patients and patients with a history of penicillin allergy who do not undergo skin testing should receive carbapenems via graded challenge.

Reliable skin tests to other classes of antibiotics, such as vancomycin or sulfonamide-type drugs, are not commercially available. However, skin testing with nonirritating concentrations of the drug may provide useful information (see Table 32.E3). This study collected data on healthy subjects without drug allergies to determine baseline nonirritating intradermal skin test concentrations for 15 commonly prescribed parenteral antibiotics. Serial 10-fold dilutions were prepared and tested in these individuals to determine the lowest dilution that did not elicit an irritant response. This concentration was then termed the nonirritating concentration (NIC). Under these circumstances, a positive skin test using the NIC of a drug suggests that the patient has drug-specific IgE antibodies and, for that reason, is at risk for a reaction and should receive an alternate, non-cross-reacting antibiotic or undergo induction of tolerance (also called desensitization). On the other hand, a negative NIC skin test result does not rule out the presence of drug-specific IgE antibodies because it is possible that a drug metabolite not present in the test reagent may be the relevant allergen.

Vancomycin may cause non-IgE-mediated histamine release and elicit immediate cutaneous erythema, flushing, and pruritus (i.e., "red man syndrome"). Slowing the rate of infusion and premedicating with histamine1 receptor antihistamines can prevent red man syndrome. Vancomycin rarely causes IgE-mediated reactions, but anaphylaxis associated with vancomycin has been reported.

A detailed history is always critical for the appropriate evaluation of allergic reactions to medications. The specific drug in question should be avoided unless life-threatening infections demand

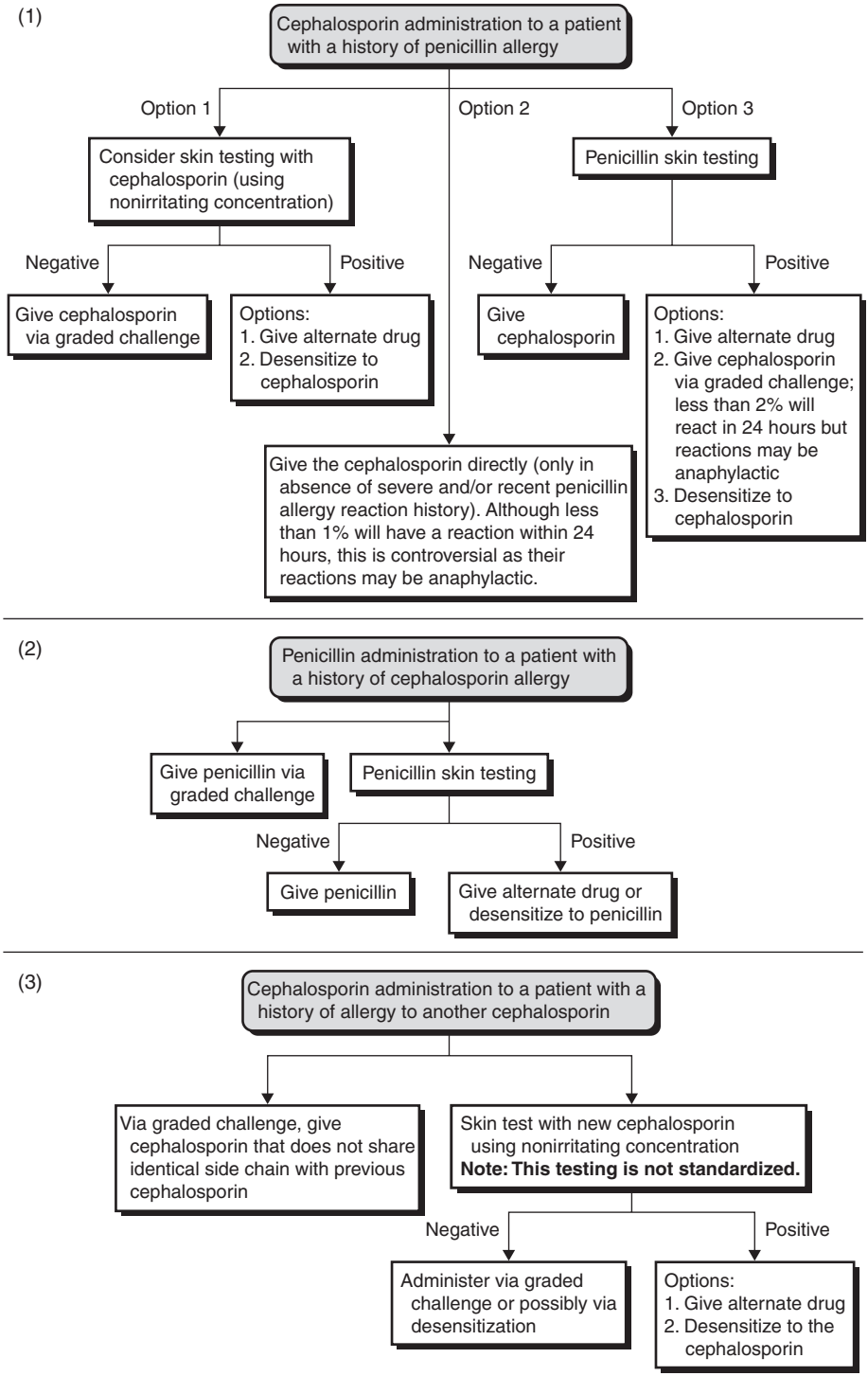


Figure 32.E1 Approach to: Panel 1. Patient with history of penicillin allergy for whom cephalosporin administration is being considered; Panel 2. Patient with history of cephalosporin allergy for whom penicillin administration is being considered; and Panel 3. Patient with history of cephalosporin allergy for whom administration of another cephalosporin is being considered. *(Adapted from Drug Allergy: Updated Practice Parameters 2010, Rolensky and Khan [eds]. Ann Allergy 105:273e1-273e78, 2010.)*

TABLE 32.E1 ■ **Groups of Beta-Lactam Antibiotics That Share Identical R_1-Group Side Chains***

Amoxicillin	Ampicillin	Ceftriaxone	Cefoxitin	Cefamandole	Ceftazidiime
Cefadroxil	Cefaclor	Cefotaxime	Cephaloridine	Cefonicid	Aztreonma
Cefprozil	Cephalexin	Cefpodoxime	Cephalothin		
Cefatrizine	Cephradine	Cefditoren			
	Cephaloglycin	Ceftizoxime			
	Loracarbef	Cefmenoxime			

*Each column represents a group with identical R_1 side chains.

Adapted from Solensky R, Khan DA, Bernstein IL, et al: Drug allergy: an updated practice parameter. Ann Allergy 2105:273e1-273e78, 2010.

TABLE 32.E2 ■ **Groups of Beta-Lactam Antibiotics That Share Identical R_2-Group Side Chains***

Cephalexin	Cefotaxime	Cefuroxime	Cefotetan	Cefaclor	Ceftibuten
Cefadroxil	Cephalothin	Cefoxitin	Cefamandole	Loracarbef	Ceftizoxime
Cephradine	Cephaloglycin		Cefmetazole		
	Cephapirin		Cefpiramide		

*Each column represents a group with identical R_2 side chains.

Adapted from Solensky R, Khan DA, Bernstein IL, et al: Drug allergy: an updated practice parameter. Ann Allergy, 105:273e1-273e78, 2010.

TABLE 32.E3 ■ **Nonirritating Concentrations of 15 Antibiotics**

Antimicrobial Drug	Nonirritating Concentration	Full-Strength Concentration	Dilution from Full Strength
Azithromycin	10 μg/mL	100 mg/mL	1:10,000
Cefotaxime	10 mg/mL	100 mg/mL	1:10
Cefuroxime	10 mg/mL	100 mg/mL	1:10
Cefazolin	32 mg/mL	320 mg/mL	1:10
Ceftazidime	10 mg/mL	100 mg/mL	1:10
Ceftriaxone	10 mg/mL	100 mg/mL	1:10
Clindamycin	15 mg/mL	150 mg/mL	1:10
Cotrimoxazole	800 μg/mL	80 mg/mL	1:100
Erythromycin	50 μg/mL	50 mg/mL	1:1000
Gentamycin	4 μg/mL	40 mg/mL	1:10
Imepenem/cilastin	0.5 mg/mL	500 mg/mL	1:10
Levofloxacin	25 μg/mL	25 mg/mL	1:1000
Meropenem	1 mg/mL	50 mg/mL	1:50
Nafcillin	25 μg/mL	250 mg/mL	1:10,000
Ticarcillin	20 mg/mL	200 mg/mL	1:10
Tobramycin	4 mg/mL	40 mg/mL	1:10
Vancomycin	5 μg/mL	50 mg/mL	1:10,000

Adapted from Empegrad R, Darter AL, Earl HS, et al: Non-irritating intradermal skin test concentrations for commonly prescribed antibiotics. J Allergy Clin Immunol 112:629-630, 2003; Solensky R, Khan DA, Bernstein IL, et al: Drug allergy: an updated practice parameter. Ann Allergy 105:273e1-273e78, 2010; and Khan D, Lecture notes from "Diagnostic Testing in Cutaneous Drug Reactions," American Academy of Allergy, Asthma & Immunology (AAAAI) Annual Meeting, 2012.

BOX 32.1 ■ Desensitization Protocol

Before Beginning Desensitization

1. Transfer the patient to an ICU or intermediate care unit so that a physician is immediately available at all times and can evaluate the patient for any reaction (wheeze, hives, and change in vital signs) before each sequential dose of antibiotic is administered.
2. Monitor and record vital signs every 15 minutes. Monitor peak flows between doses in patients with bronchospastic pulmonary disease.
3. Provide adequate intravenous (IV) access (preferably 2 IV lines 16-gauge or larger). Optimize the patient's hemodynamic status and avoid use of beta-blockers.
4. Ensure that epinephrine, IV diphenhydramine, and methylprednisolone are at the bedside. Equipment and drugs for tracheal intubation should be readily accessible.
5. Obtain informed consent from the patient or appropriate surrogate decision maker.
6. Do *not* premedicate the patient with antihistamines or steroids.

Preparation of Dilutions

After the specific antibiotic and dose (e.g., ceftriaxone 1g) is decided on and the desired final dose is calculated, serial 10-fold dilutions of that dose in 50 mL of normal saline should be made:
Dilution 1: 1×10^{-6} concentration of the final dose in 50 mL normal saline
Dilution 2: 1×10^{-5} concentration of the final dose in 50 mL normal saline
Dilution 3: 1×10^{-4} concentration of the final dose in 50 mL normal saline
Dilution 4: 1×10^{-3} concentration of the final dose in 50 mL normal saline
Dilution 5: 1×10^{-2} concentration of the final dose in 50 mL normal saline
Dilution 6: 1×10^{-1} concentration of the final dose in 50 mL normal saline
Dilution 7: Full strength final dose in 50 mL normal saline

Administration of Dilutions

1. 50 mL of each dilution, starting with dilution 1, should be administered intravenously over 20 minutes.
2. After completion of the dose, the patient should be observed for 15 minutes and be evaluated by a physician.
3. If no reaction has occurred, the next dose can be given in the same manner.
4. If an adverse reaction occurred, follow recommendations in Table 32.2.

Adapted from Weiss ME, Adkinson NF: Immediate hypersensitivity reactions to penicillin and related antibiotics. Clin Allergy 18:515-540, 1988.

its use and an induction of tolerance procedure (also called desensitization) would then be necessary. In situations where there is a definite need for a particular medication and no alternative medication is available, induction of tolerance should be considered. This procedure involves the administration of incremental doses of the drug, which temporarily allow tolerance to the drug. As in skin testing, induction of drug tolerance should almost never be performed if the reaction history includes a severe non-IgE-mediated reaction such as Stevens-Johnson syndrome (SJS); toxic epidermal necrolysis (TEN); drug rash, eosinophilia, and systemic symptoms (DRESS); hepatitis; or hemolytic anemia.

Management of Patients with Positive Skin Test Results to Penicillin

If a patient with a positive penicillin skin test result requires therapy with a beta-lactam or cephalosporin to treat a life-threatening infection because no other effective alternative antibiotic is

TABLE 32.2 ■ **Management of Adverse Reactions during Desensitization**

Reaction Severity	Symptoms and Signs	Management
Mild	Mild urticaria *without* hemodynamic instability, respiratory distress, or angioedema	The last dilution tolerated *without* difficulty should be repeated and the protocol continued if no further reaction occurs.
Moderate	Chest tightness, diffuse hives, but no hemodynamic or airway compromise	Administer 0.3 mL 1:1000 epinephrine (0.3 mg) subcutaneously. If the patient's symptoms resolve within 30 min, the last dilution tolerated *without* a reaction should then be repeated and the protocol continued if no further reaction occurs.
Moderate to severe	Diffuse wheezes, throat tightness	Administer epinephrine as described above. Epinephrine can be repeated every 15 min if required. If the reaction is severe, 0.5–1.0 mg of 1:10,000 epinephrine can be given IV every 5 min. If the symptoms subside quickly and if the antibiotic is considered to be *absolutely necessary* to adequately treat the patient, *one-half* the dose of the last tolerated dilution should be given with a physician at the bedside.* Desensitization can then be continued if this dose is tolerated without reaction.
Severe	Hypotension, laryngeal edema with or without urticaria	Treat with epinephrine as above, and give IV: 50 mg diphenhydramine, a histamine H_2 receptor blocker, and corticosteroids (60 mg of methylprednisolone). The desensitization protocol must be discontinued.

*For example, if dilution 4 (1×10^{-3} concentration of the final dose) in Box 32.1 was the last tolerated dose, administer 0.5×10^{-4} concentration of the final dose in 50 mL normal saline.

Adapted from Sheffer AL, Pennoyer DS: Management of adverse drug reactions. J Allergy Clin Immunol 74:580-588, 1984.

available, induction of tolerance can be attempted. Patients who cannot undergo skin testing or who do not react appropriately to controls should also be desensitized if beta-lactams are required. Desensitization with other antibiotics, such as vancomycin and trimethoprim-sulfamethoxazole, has also been performed successfully in patients who were at high risk for an anaphylactic reaction to these drugs. However, sulfonamide antibiotics rarely cause IgE-mediated reactions. A more common presentation is a delayed maculopapular rash, especially in patients with human immunodeficiency virus infection. As previously indicated, *an absolute contraindication to desensitization* is a history of exfoliative dermatitis to the chosen antibiotic.

Successful desensitization induces temporary immunologic tolerance and significantly reduces the risk of anaphylaxis to the drug, but it has no effect on the incidence of other non-IgE-mediated reactions. This tolerance to the specific antibiotic persists only while the patient continues to receive it. Once therapy ceases for a period greater than 24 hours, the patient is again at risk for an immediate, IgE-mediated reaction and, therefore, would require desensitization again.

Desensitization can be performed either orally or parenterally. However, because the oral route is often difficult or impossible to use in the patient in the ICU, intravenous (IV) desensitization is the preferred method of desensitization in that setting. Patients may experience an allergic reaction during desensitization or during the treatment course that follows. Although most are

mild, serious reactions have been reported. Late immunologic reactions such as serum sickness may also occur.

Protocols for desensitization (Box 32.1, Table 32.E4) and managing adverse reactions during this procedure (Table 32.2) have been adapted from methods reported in the literature.

An annotated bibliography can be found at www.expertconsult.com.

TABLE 32.E4 ■ **Example of Intravenous Cephalosporin IgE Induction of Drug Tolerance Protocol (a full dose equals 1000 mg; total time was 349.4 minutes [5.8 hours])**

Preparation of Solutions

Volume of diluent (e.g., 0.9% sodium chloride)

Total to be injected in each bottle

Final concentration, mg/mL

Solution 1: 250 mL containing 10 mg = 0.04 mg/mL

Solution 2: 250 mL containing 100 mg = 0.4 mg/mL

Solution 3: 250 mL containing 1000 mg = 4 mg/mL

Step	Solution	Rate (mL/h)	Time (min)	Administered Dose (mg)	Cumulative Dose (mg)
1	1	2	15	0.02	
2	1	5	15	0.07	
3	1	10	15	0.17	
4	1	20	15	0.37	
5	2	5	15	0.87	
6	2	10	15	1.87	
7	2	20	15	3.87	
8	2	40	15	7.87	
9	3	10	15	17.87	
10	3	20	15	37.87	
11	3	40	15	77.87	
12	3	75	184.4	922.13	1000

Modified from Solensky R, Khan DA, Bernstein IL, et al: Drug allergy: an updated practice parameter. Ann Allergy 105:273e1-273e78, 2010.

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Cotliar J: Approach to the patient with a suspected drug eruption. Semin Cutan Med Surg 26:147-154, 2007.

This article (by a dermatologist) reviews serious adverse drug eruptions such as drug rash, eosinophilia, systemic symptoms (DRESS), Stevens-Johnson syndrome, and toxic epidermal necrolysis (TENS).

Empegrad R, Darter AL, Earl HS, et al: Non-irritating intradermal skin test concentrations for commonly prescribed antibiotics. J Allergy Clin Immunol 112(3):629-630, 2003.

This study was designed to help evaluate patients with histories of drug-induced reactions with antibiotics that do have validated skin tests and that have features consistent with an IgE-mediated process. The study collected data on healthy subjects without drug allergies to determine baseline nonirritating intradermal skin test concentrations for 15 commonly prescribed parenteral antibiotics. If in lyophilized form, antibiotics were reconstituted according to the instructions in the package insert; either saline or sterile water was used as the diluent as recommended by the manufacturer. Reagents were prepared fresh on the day of testing. Serial 10-fold dilutions were prepared and tested in this individual to determine the lowest dilution that did not elicit an irritant response. This concentration was then termed the nonirritating concentration (NIC). They were unable to establish a nonirritating concentration for ciprofloxacin. A positive skin test using the NIC of a drug suggests that the patient has drug-specific IgE antibodies and, for that reason, is at risk for an allergic anaphylactic reaction. On the other hand, a negative skin test result does not rule out the presence of drug-specific IgE antibodies.

Green GR, Rosenblaum AH, Sweet LC: Evaluation of penicillin hypersensitivity: value of clinical history and skin testing with penicilloyl-polylysine and penicillin G. J Allergy Clin Immunol 60:329-345, 1977.

This landmark study evaluated the utility of penicillin skin tests.

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Solensky R, Earl HS, Gruchalla RS: Penicillin allergy: prevalence of vague history in skin test-positive patients. Ann Allergy Asthma Immunol 85:195-199, 2000.

This article reviewed the published literature to determine how many patients who had a history of penicillin (PCN) allergy and were skin test positive had a vague history of PCN allergy. Overall, 347/1063, or 32%, of history positive/skin test–positive patients had a vague PCN allergy history, with a range of 0% to 70% among the 30 studies. Researchers concluded that, like patients with convincing histories, patients with vague allergic histories should undergo PCN skin testing prior to PCN administration.

Solensky R, Khan DA, Bernstein IL, et al: Drug allergy: an updated practice parameter. Ann Allergy 105:273e1-273e78, 2010.

This document was written and reviewed by specialists in the field of allergy and immunology and was exclusively funded by the three national allergy and immunologic societies: the American Academy of Allergy, Asthma and Immunology (AAAAI); the American College of Allergy, Asthma and Immunology (ACAAI); and the Joint Council of Allergy, Asthma and Immunology (JCAAI). This document may be accessed under the AAAAI website (www.AAAAI.org), under Practice Resources, Statements and Practice Parameters, Drug Allergy: an updated practice parameter (2010). It can be retrieved at http://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/drug-allergy-updated-practice-param.pdf. (Accessed August 9, 2012.)

Valyasevi MA, Van Dellen RG: Frequency of systematic reactions to penicillin skin tests. Ann Allergy Asthma Immunol 85(5):363-365, 2000.

This study is a retrospective chart review of 1710 patients with a history of penicillin allergy who underwent skin testing with major and minor (penicillin G) determinants (prick tests and intradermal). Eighty-six patients had a positive skin test and two patients had a systemic reaction. Neither patient required hospitalization; one responded well to treatment with epinephrine and the other to chlorpheniramine maleate and prednisone. The systemic reaction rate was 0.12% for all patients and 2.3% for the penicillin skin test–positive group. No fatalities occurred.

CHAPTER 33

Arrhythmias (Bradycardias)

Suraj Kapa ■ David Callans

Bradyarrhythmias, or slow heart rhythms, occur commonly in patients treated in the intensive care unit (ICU). Assessment of the critically ill patient with a bradyarrhythmia needs to take into account the clinical context and whether or not the bradyarrhythmia is causing either significant symptoms or hemodynamic compromise. Bradyarrhythmias may reflect physiologic (e.g., high vagal tone) or pathologic (e.g., high grade conduction system disease) conditions. Usually these arrhythmias resolve spontaneously or after treating the underlying cause. However, rarely, either temporary (such as a temporary pacing wire or chronotropically stimulating drugs) or permanent (such as a permanent pacemaker) interventions may be required. This chapter provides a concise approach to the ICU patient presenting with bradyarrhythmias. Bradyarrhythmias in the setting of acute myocardial infarctions are discussed in Chapter 50.

Definitions

Bradyarrhythmias refer to any disturbance in the heart rhythm in which the heart rate is abnormally slowed. Bradycardia, meanwhile, is grossly defined as any heart rate < 60 beats per minute. The limitation in using an absolute cutoff for the heart rate in categorizing pathologic arrhythmias is that a heart rate < 60 beats per minute may be physiologic and not a cause for concern in many patients. However, some patients may have a ventricular rate > 60 beats per minute, which may nevertheless be insufficient for their physiologic demands. Thus, "pathologic" bradyarrhythmias should include any heart rate that is either insufficient to meet physiologic demands, resulting in either symptoms or hemodynamic compromise, or that is associated with a high risk of progressing to a rhythm that may result in sudden death or hemodynamic collapse.

Approach to the Patient Presenting with a Bradyarrhythmia

When a patient presents with a slow heart rhythm, whether symptomatic or not, consideration must be first given to the clinical context as well as to classifying the mechanism of the arrhythmia. The clinical context is important because, in most patients, the bradyarrhythmia may be transient, such as that caused by high vagal tone during nasogastric suctioning or a hypoxic episode, or may result from cardioactive drugs, in which case the bradyarrhythmia may resolve after withdrawal of the offending agent. Sometimes, self-limited causes of a bradyarrhythmia may be identified but not readily reversible, and supportive, temporary interventions may be needed while the underlying cause resolves. In other cases, even though the underlying cause may be identified, the situation may not be reversible because of a clinical need of the offending agent to treat another condition or because of a lack of available therapies to "cure" the associated condition, and permanent interventions, such as implantation of a permanent pacemaker, may be needed.

In terms of diagnosing the mechanism, or the underlying disturbance in the conduction system leading to the bradyarrhythmia, all available resources in the ICU for documenting and reviewing the rhythm should be used. The primary ways in which the heart rate and rhythm are

recorded in the ICU include pulse checks and telemetry. The limitations of each and alternative methods of diagnosing the electrophysiologic mechanism of the arrhythmia need to be considered in order to optimize decision making. In the case of pulse checks, the recorded heart rate while palpating the radial, femoral, or carotid pulse may not always reflect the number of times the heart is electrically depolarizing. For example, frequent nonperfused premature ventricular contractions may result in a QRS complex on telemetry or electrocardiography that is not noted while palpating the pulse (Figure 33.1). Thus, a pulse check in the absence of corresponding telemetry may be ineffective in establishing the diagnosis of a bradyarrhythmia in the absence of corresponding electrocardiogram (ECG) recordings.

In turn, telemetry offers one to three lead recordings of ECG activity. Review of telemetry alarms affords the ability to identify pauses, or periods of absence of any cardiac electrical activity, the mechanism of the pauses depending on whether the absence of activity occurs solely at the ventricular or at both the ventricular and atrial levels, and the periods immediately before and after the arrhythmia. Telemetry may be used in a similar fashion to assess periods where the heart rhythm is slowed. The episode of bradycardia needs to be further correlated with simultaneous blood pressure recordings and time of day in order to determine if there is any association with symptoms.

In some patients, because of inability to adequately see atrial activity on the limited leads available on telemetry or because of noise on telemetry that may impede interpretation, a full



Figure 33.1 Frequent nonperfused premature ventricular contractions. Note the six leads of electrocardiogram (ECG) at the top and the arterial pressure tracing below. The sinus beats are perfused and result in an arterial pulsation, but the premature ventricular contractions (PVCs) do not result in a significant arterial pulsation. Thus, the effective *pulse* rate is 35 beats per minute even though the ECG heart rate as defined by the number of electrical depolarizations occurring within a minute on ECG is ~70 beats per minute. Recording of heart rate by pulse would thus result in a finding of bradycardia that may not correlate with the number of times the ventricle electrically depolarizes per minute and thus would be insufficient to define the cause of the low pulse rate.

12-lead ECG may be needed to diagnose the mechanism of the bradyarrhythmia. However, telemetry is generally sufficient to identify and diagnose the arrhythmia mechanism.

Once the bradyarrhythmia has been documented, classification of the bradyarrhythmia via a detailed analysis of the ECG findings is key. However, proper classification requires close, expert review of all strips with an orderly approach that involves reviewing the atrial and ventricular rhythms, identifying changes in morphology of atrial or ventricular beats that would suggest depolarizations emanating from ectopic foci, and correlating each atrial and ventricular beat to document association versus dissociation.

Classification of Bradyarrhythmias

Bradyarrhythmias may result from dysfunction of the sinus node or disturbances of atrioventricular (AV) conduction. The classification of bradyarrhythmias principally relies on documentation of a slow *ventricular* rate, which may or may not be generated due to a slow atrial rate. When classifying bradyarrhythmias, one should first identify the electrophysiologic mechanism and secondly whether or not a drug or another clinical event is causing the rhythm.

SINUS NODE DYSFUNCTION

The spectrum of sinus node dysfunction encompasses sinus pauses, sinus arrest, sinus bradycardia, sinus node exit block, and the tachycardia-bradycardia syndrome (sick sinus syndrome). All may result in bradycardia or pauses caused by the lack of impulse formation or propagation from the sinus node. Occasionally, not only does the sinus node fail, but "backup" subsidiary pacemakers (atrial and junctional) may also fail, and appropriate heart rate is not maintained.

Causes of sinus node dysfunction in ICU patients are listed in Box 33.1. It is important to recognize that sinus bradycardia is commonly seen in young athletic patients, during sleep, and during conditions associated with high vagal tone (pain, nausea, vomiting, endotracheal manipulation, bowel movements). These episodes are almost uniformly transient and asymptomatic. Treatment should be considered only if the bradycardia persists, is symptomatic, or results in hemodynamic compromise and the underlying cause is expected to recur or cannot be withdrawn.

In patients with preexisting heart disease, sinus node dysfunction may present with significant hemodynamically compromising bradyarrhythmias, particularly in the ICU setting. Ischemia, electrolyte abnormalities, drugs, hypoxia, and metabolic and endocrinologic derangements may all precipitate a clinically significant bradycardia in patients with chronic, previously stable sinus node disease. Patients with severe left ventricular systolic dysfunction are also at risk of significant sinus bradyarrhythmias, particularly in the setting of worsening heart failure. Furthermore, because inappropriately slow sinus rates may be causally related to heart failure symptoms, permanent pacing has a role in the management of these patients.

Sinus node dysfunction, particularly in the elderly, may also be associated with tachycardia-bradycardia syndrome in which symptoms may be related to the tachy- or bradyarrhythmia. Tachycardia-bradycardia syndrome is characterized by periods of atrial tachyarrhythmias (atrial flutter, atrial tachycardia, or atrial fibrillation [see Chapter 34]) interspersed with periods of sinus bradycardia or sinus arrest. Tachycardia-bradycardia syndrome is most often seen in the setting of paroxysmal atrial fibrillation when a prolonged sinus recovery time upon termination of the atrial fibrillation episode may lead to a sinus pause ("offset pause") or a period of sinus bradycardia. Rarely, these pauses may result in syncope. Because symptoms can be due to either tachycardia or bradycardia, treatment consisting of both medication to control the fast heart rates and permanent pacing to prevent slow heart rates may be required in these patients.

BOX 33.1 ■ Common Causes of Bradyarrhythmias in the Intensive Care Unit

Extrinsic Causes

- Carotid sinus hypersensitivity
- Drugs
  - Antiarrhythmic agents (procainamide, propafenone, amiodarone)
  - Beta-adrenergic blockers
  - Calcium channel blockers
  - Digoxin
  - Morphine
  - Tricyclic antidepressants
- Elevated intracranial pressure
- Electrolyte abnormalities (hyperkalemia, hypokalemia, hypocalcemia, hypermagnesemia)
- High vagal tone (mechanical ventilation, myocardial ischemia-infarction, nausea, vomiting, pain, sleep, vasovagal reflex)
- Hypothermia
- Hypothyroidism
- Hypoxia
- Obstructive sleep apnea

Intrinsic Causes

- Collagen vascular disease (systemic lupus erythematosus, rheumatoid arthritis, scleroderma)
- Conduction system disease
- Congenital heart disease (e.g., atrial septal defect)
- Hypertensive heart disease
- Infections (endocarditis, Lyme disease, viral myocarditis, diphtheria)
- Infiltrative cardiomyopathy
- Intrinsic sinus node disease
- Myocardial ischemia or infarction
- Sarcoidosis
- Valvular heart disease (aortic stenosis, aortic insufficiency, mitral annular calcification)

ATRIOVENTRICULAR CONDUCTION DISTURBANCES

Disturbances of propagation of electrical impulses from the atria to the ventricles are classified as being secondary to different degrees of atrioventricular (AV) block (first, second, or third degree). This classification is based on the electrocardiographic pattern of the conduction disturbance which, in turn, is used to correlate with the anatomic substrate. Block occurring in the AV node generally signifies a more benign prognosis than does block resulting from disease of infranodal structures (e.g., the His-Purkinje system). Although intrinsic cardiac disease can lead to AV conduction disturbances, reversible extrinsic causes should be sought before interventions are considered (see Box 33.1). Depending on how readily the extrinsic cause may be reversed, temporary interventions to treat the bradyarrhythmia may be required. Except in cases of higher-grade conduction block at high risk of progressing to complete heart block or asystole (discussed later), acute intervention (pharmacologic or pacing) should generally be reserved for patients who are symptomatic or hemodynamically compromised. The anatomic site of block is relevant in defining which patients should receive a permanent pacemaker. However, the ultimate decision on the need for treatment is based on the presence of symptoms attributable to the bradyarrhythmia.

First-Degree Atrioventricular Block

First-degree AV block, defined as a PR interval > 200 milliseconds, rarely results in symptoms or significant hemodynamic compromise. It is most often due to delay of the electrical impulse



Figure 33.2 Atrioventricular Wenckebach (second-degree atrioventricular [AV] block, Mobitz I) with 4:3 AV conduction. P waves marked with *. Note progressive prolongation in PR interval before blocked P wave. This pattern suggests the site of block is in the AV node and implies no risk of progression to complete heart block.

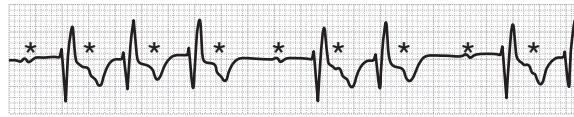


Figure 33.3 Mobitz II block. P waves marked with *. Note that the PR interval does not change on the conducted beats and the baseline bundle branch block, suggesting infra-Hisian conduction disease. This rhythm has a high risk for progression to complete heart block and would generally indicate the need for implantation of a permanent pacemaker.

as it traverses the AV node. Disease of the His-Purkinje system can occasionally prolong the PR interval, though generally its contribution to the PR interval is negligible. Because every impulse originating in the sinus node propagates to the ventricle, first-degree AV *delay* is a more accurate description of this phenomenon.

In many patients, the length of the PR interval may correlate with the heart rate. Thus, at higher heart rates the PR interval may be longer. If the PR interval is sufficiently long, patients may experience a condition where atrial depolarization occurs immediately after or concurrent with ventricular depolarization. When this happens, patients may experience headache, heart failure symptoms, or hypotension. This phenomenon is similar to that seen in patients with pacemakers in whom a "pacemaker syndrome" may occur as a result of atrial contraction occurring at a time concurrent with ventricular depolarization rather than after ventricular relaxation. In these patients, permanent pacing may be useful to better coordinate atrial and ventricular depolarization.

Second-Degree Atrioventricular Block

Second-degree AV block is divided into Mobitz I block (Wenckebach) and Mobitz II block. *Mobitz I block* is characterized as progressive prolongation of the PR interval until a P wave fails to propagate to the ventricle (Figure 33.2). Because the incremental PR prolongation decreases with each consecutive beat, the RR intervals progressively shorten during Mobitz I block. Generally, the simplest mechanism by which to diagnose Mobitz I block is to compare the PR interval of the beat conducted immediately *after* the skipped beat with the PR interval of the beat conducted immediately *before* the skipped beat, as successive PR intervals may only show gradual prolongation. The presence of Mobitz I block generally indicates that the site of block is in the AV node, thus portending a more benign prognosis. However, Mobitz I block can rarely occur in the infranodal structures, though intracardiac recordings are required for this diagnosis. Permanent pacemaker implantation is indicated only in patients in whom Wenckebach block has been demonstrated to cause symptoms.

Mobitz II block is defined as the sudden failure of conduction of an impulse from the atria to the ventricles and manifests on the ECG as unexpected block of a P wave without the progressive prolongation of the PR interval seen with preceding beats (Figure 33.3). Mobitz II block signifies infranodal disease and often is associated with other electrocardiographic signs of conduction system disease (e.g., bundle branch block or intraventricular conduction delays). Although a permanent pacemaker may not be absolutely indicated for patients with asymptomatic Mobitz



Figure 33.4 2:1 Atrioventricular block. P waves marked with * (ECG V1 lead). **A,** Block at the level of the AV node. Note the narrow QRS and long PR interval on conducted beats. Block in the AV node is usually mediated by autonomic tone and does not imply a risk of progressive block. **B,** Block at the infranodal level (His-Purkinje). Note the wide QRS (right bundle branch block), signifying significant distal conduction system disease, and normal PR interval on conducted beats. Patients with infranodal 2:1 block have a significant risk for the development of higher-degree AV block.

II block, there is a risk of a sudden loss of atrioventricular conduction and, if this happens, a ventricular escape rhythm may or may not be present. Thus, the majority of patients do receive pacemakers given the relatively high risk (40% to 80%) of progression to higher-grade AV block. In particularly high-risk patients, a temporary pacing wire may be appropriate until a permanent pacemaker can be implanted.

Patients with 2:1 AV block, in whom every other P wave is associated with a QRS complex, may be difficult to classify as either Mobitz I or II block because there is no opportunity for the PR interval to become prolonged with successive beats (Figure 33.4). The site of block in these patients may be either AV nodal or infranodal. Clues on the ECG that suggest an infranodal site include a wide QRS (> 120 msec) on the conducted beats or an associated bundle branch or fascicular block. Furthermore, a normal PR interval on the conducted beats may support the presence of infranodal disease. In these patients, the effective heart rate (defined by the ventricular rate) is half that of the atrial rate. Findings suggestive of infranodal disease or the presence of associated symptoms should prompt consideration of placement of a temporary pacemaker and, ultimately, a permanent pacemaker in those without a definite reversible cause.

When the site of conduction block is ambiguous, electrophysiologic evaluation with intracardiac recordings from the His bundle may be obtained. Specific measurements during this evaluation (e.g., the time between the His signal on an intracardiac electrode recording and the ventricular signal [i.e., the HV interval], the response to rapid atrial pacing, etc.) may provide additional information that is helpful in identifying patients who require permanent pacing.

Third-Degree Heart Block

Third-degree heart block, or complete heart block, is defined as the complete absence of impulse propagation from the atria to the ventricles. The ECG manifestation of complete heart block includes AV dissociation, a regular junctional or ventricular escape rhythm, and an atrial rate that is faster than the ventricular rate. All three of these criteria need to be present in order to diagnose complete heart block. In the absence of reversible causes, complete heart block suggests severe

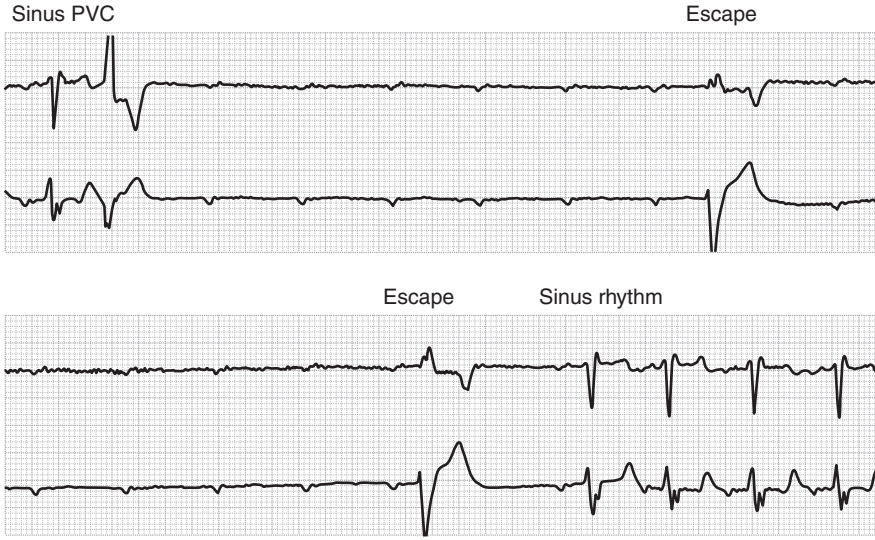


Figure 33.5 Phase IV block or paroxysmal complete heart block. Note the sinus beat followed by a premature ventricular contraction in the top tracing. Likely because of retrograde penetration of the His bundle resulting in a change in the normal phase IV portion of the action potential, there is subsequent block with P waves and no associated QRS complexes. Two ventricular escape beats are visible prior to restoration of normal sinus rhythm. Onset of this rhythm is unpredictable and may result in syncope, thus indicating need for a pacemaker.

conduction disease and, with rare exceptions, implantation of a permanent pacemaker should be performed.

One example of transient complete heart block that should prompt immediate referral for either a temporary pacemaker or, if readily available, a permanent pacemaker is the presence of phase 4 block, or bradycardia-dependent block. In this form of block, an atrial, junctional, or ventricular extrasystole may precipitate a period in which there is complete loss of conduction of atrial stimuli to the ventricle. This appears on the ECG as a series of P waves without associated QRS complexes (Figure 33.5). The mechanism of block is poorly understood but involves fluctuations in phase 4 of the action potential associated with changes in the frequency of electrical stimuli reaching the His bundle. The onset of heart block resulting from extrasystoles is unpredictable, and thus a single episode of phase 4 block should immediately prompt referral for either the placement of prophylactic transcutaneous pads in case of a recurrent episode or placement of a transvenous pacing wire until a permanent pacemaker can be placed.

Bradyarrhythmias under Special Circumstances

AFTER CARDIAC SURGERY

Patients are at high risk for the development of both tachyarrhythmias and bradyarrhythmias during the early postoperative period after cardiac surgery. Transient postoperative conduction disturbances have been reported in up to half of patients undergoing cardiac surgery with most of these being isolated right or left bundle branch block. Because of the high occurrence of these conduction disturbances, temporary epicardial pacing wires are routinely placed in all patients during surgery. These wires are typically removed 3 to 7 days after surgery, provided that the patient is stable.

The development of postoperative conduction disturbances appears to be related to multiple preoperative and intraoperative factors. *Clinical characteristics* associated with their development include advanced age, hypertension, coronary anatomy, left ventricular function, use of digoxin, and the presence of preexisting conduction abnormalities. *Intraoperative factors* include the number of bypass grafts, duration of aortic cross-clamp time, concomitant valve surgery, and the type of cardioplegia used. Specifically, the use of cold cardioplegia intraoperatively has been shown to have a dramatic impact on the development of postoperative conduction disturbances. A significantly higher incidence of conduction abnormalities at hospital discharge has been found in patients who had received cold compared with warm cardioplegia (19.6% versus 1.7%, respectively). Furthermore, these defects persist in 17.4% and 1.7% of patients, respectively, at late follow-up.

Fortunately, the majority of postoperative conduction disturbances resolve spontaneously, and permanent pacemaker insertion is rarely required. In a large cohort of 1645 patients who underwent coronary artery bypass grafting (CABG), only 13 patients (0.8%) required permanent pacemaker implantation for persistent complete AV block (8 patients) or symptomatic sinus node dysfunction (5 patients). These pacemakers were implanted at a mean of 10.5 ± 6.5 days after surgery.

It is unclear whether the development of fascicular conduction disturbances postoperatively (bundle branch block, fascicular block, or intraventricular block) is associated with decreased long-term survival. Early reports demonstrated a significantly higher mortality in patients who developed left bundle branch block (LBBB), left anterior fascicular block (LAFB), or intraventricular conduction delays after CABG compared with patients in whom these abnormalities did not develop. Subsequently larger studies failed to confirm these findings. Although development of new conduction abnormalities postoperatively does appear to be associated with a higher mortality, these patients also have a higher incidence of perioperative myocardial infarction and low cardiac output states. Therefore, it may be that these abnormalities are merely markers of already present cardiac dysfunction.

The incidence of heart block occurring after valve replacement or repair is higher than after CABG. Generally, those patients at highest risk of developing complete heart block are those with a preexisting conduction system disturbance. For example, patients with preexisting right bundle branch block are at higher risk of complete heart block after surgery on left-sided valves, whereas those with preexisting left bundle branch block are at higher risk after surgery on right-sided valves. This is because of the proximity of the valvular structures to the His bundle and central components of the conduction system on the corresponding side of the heart. Thus, any valve repair or replacement, whether interventional, such as transcatheter aortic valvular interventions (TAVI), or surgical, may increase risk of heart block. The risk of heart block also increases with the number of prior surgeries (e.g., in the setting of "redo" valve surgery) and the number of valves being replaced.

The assessment of patients presenting with heart block after cardiac surgery requires that one consider when the episode of heart block occurs after surgery. Complete heart block that occurs immediately after surgery, resolves over hours to days, and does not recur may simply be due to edema and not be associated with long-term risk of heart block. However, complete heart block that occurs after a period of normal conduction postoperatively incurs a higher risk of future heart block. Thus, identifying periods of conduction interspersed with periods of complete heart block is important when determining need for pacemaker implantation.

Patients in whom symptomatic bradyarrhythmias develop in the early postoperative period should be supported acutely with pacing via the temporary epicardial wires placed during the operative procedure. Placement of transvenous temporary pacing wires should be considered only in patients who are truly pacemaker dependent and in whom a permanent pacemaker cannot yet be placed (e.g., because of infection) and the epicardial wires are not functioning properly (e.g., because of excessively high thresholds). Discontinuation of agents that depress the cardiac

chronotropic response (digoxin, beta-blockers, calcium channel blockers, and the antiarrhythmic drugs listed in Box 33.1) should be considered. Determination of the pacing threshold of either temporary epicardial or transvenous pacing wires should be performed daily. As most of the conduction disturbances are transient, daily assessment of the patient's native rhythm should be performed as well. Generally, 5 to 7 days should be allowed for recovery of function before a permanent pacemaker is considered.

ENDOCARDITIS

Bacterial endocarditis is frequently seen in the ICU setting. The development of conduction disturbances in a patient with endocarditis is an ominous sign and suggests deep invasion of the infection into the perivalvular tissue. Conduction disturbances occur in ~10% of patients with endocarditis, of whom 80% to 90% have perivalvular abscesses. Disturbances in AV conduction most often complicate infection of the aortic valve and carry a higher mortality. Daily ECGs during treatment of patients with valvular endocarditis, particularly aortic valve endocarditis, should be performed to evaluate for subtle changes in AV conduction. Progressive prolongation of the PR interval over days even in the absence of higher degrees of AV block, for example, may suggest further extension of infection. The development of any new conduction disturbance such as higher-degree heart block or a bundle branch or fascicular block in a patient with documented or suspected endocarditis should prompt immediate evaluation with a transthoracic or transesophageal echocardiogram, or both. Urgent surgical consultation is indicated, and valve replacement should be strongly considered in these patients. Surgery should not be delayed, even in patients with "active" infection, when there is evidence of new or progressive conduction abnormalities, as most studies have demonstrated better survival and a lower reinfection rate with earlier surgical intervention.

Obstructive Sleep Apnea

Arrhythmias are common in patients with obstructive sleep apnea (see Chapter 80). These arrhythmias are often discovered serendipitously in the ICU during routine cardiac monitoring and frequently prompt cardiac evaluation. The spectrum of arrhythmias associated with obstructive sleep apnea includes isolated premature ventricular contractions, nonsustained ventricular tachycardia, sinus bradycardia, sinus pauses, and second-degree AV block (Mobitz I and II). They are generally seen during episodes of hypoxemia while the patient is sleeping (Figure 33.6). The mechanism of these arrhythmias is likely due to an autonomic nervous system imbalance caused by arterial oxygen desaturation.

A corollary of this condition is seen with the diving reflex, when prolonged apnea causes increases in sympathetic tone to the peripheral blood vessels and increased vagal drive to the heart, leading to a slow heart rate while maintaining normal blood pressure. Prolonged sinus pauses (> 10 seconds) and severe sinus bradycardia (< 30 beats/minute for > 10 seconds) can be seen in these patients, and this frequently leads to consideration of permanent pacemaker implantation. However, unless

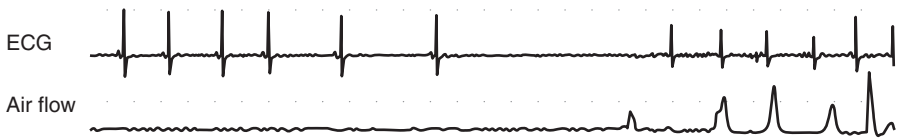


Figure 33.6 Sinus bradycardia and sinus arrest during an apneic period in a patient with obstructive sleep apnea. Note the progressive slowing of the heart rate in the ECG recording (ECG, *top*) and the lack of airflow noted during the polysomnography study in the bottom tracing. With restoration of respirations toward the end of the tracing there is restoration of the heart rate.

there is evidence of significant cardiac disease or documented symptomatic bradycardia while the patient is awake, permanent pacing is rarely indicated because these arrhythmias almost universally resolve with appropriate treatment of the sleep apnea and have not been specifically correlated with negative outcomes.

DIGOXIN TOXICITY

Digoxin is commonly used in patients with heart failure and for rate control in patients with atrial tachyarrhythmias. Toxicity can present with both cardiac and extracardiac signs and symptoms. Cardiac manifestations of toxicity may manifest as either decreased AV conduction or increased automaticity (Box 33.2). Generally, patients *without* structural heart disease present with bradyarrhythmias resulting from depressed impulse conduction, whereas patients *with* preexisting heart disease exhibit tachyarrhythmias because of abnormalities of both impulse conduction and generation. Unfortunately most of these arrhythmias are not specific for digoxin toxicity, and therefore the development of one of these arrhythmias in a patient taking digoxin is suggestive but not diagnostic of toxicity.

Atrioventricular conduction block is the most common manifestation of toxicity, occurring in 30% to 40% of patients presenting with arrhythmias secondary to digoxin toxicity. Specific arrhythmias that are uncommon but specific for digoxin toxicity include atrial tachycardia with variable AV block, accelerated junctional rhythm resulting in the apparent "regularization" of atrial fibrillation (Figure 33.7), and fascicular tachycardia. The development of any of these arrhythmias should heighten the suspicion of toxicity from digoxin, regardless of the serum digoxin level.

The extracardiac manifestations of digoxin toxicity are nonspecific but usually present. Nausea, vomiting, and anorexia, the most common symptoms, are seen in almost half of patients presenting with toxicity. Other symptoms may include dizziness, fatigue, abdominal pain, and headache. Visual disturbances characterized by halos around bright objects and changes in color perception have been described with digoxin toxicity but occur in less than 10% of patients.

BOX 33.2 ■ Arrhythmias Associated with Digoxin Toxicity

Nonspecific arrhythmias
- Sinus bradycardia
- Sinus exit block
- Atrioventricular conduction disturbances
- Ventricular ectopy
- Ventricular fibrillation

Specific arrhythmias
- Atrial tachycardia with variable atrioventricular block
- Accelerated junctional rhythm during atrial fibrillation (i.e., regularized rate during atrial fibrillation)
- Fascicular tachycardia
- Bidirectional ventricular tachycardia

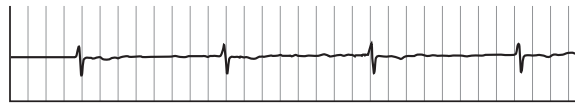


Figure 33.7 Digoxin toxicity. Baseline rhythm is atrial fibrillation (undulating baseline consistent with fibrillatory activity) with complete heart block and junctional escape rhythm at 30 beats per minute. The ventricular response during atrial fibrillation is always irregular. The sudden "regularization" of the ventricular response during atrial fibrillation is highly suggestive of digoxin toxicity, particularly if the heart rate is slow, as in this case.

Although studies conducted in the 1960s and 1970s estimated that ~20% of patients receiving maintenance digoxin therapy acquired signs or symptoms of toxicity at some point in their clinical course, a prospective trial of 563 patients admitted to the hospital between 1980 and 1988 with heart failure who were taking digoxin found definitive evidence of toxicity in only 4 patients (0.8%). Despite the dose-related therapeutic and toxic effects of digoxin, the correlation between digoxin serum levels and clinical toxicity is poor and varies considerably from patient to patient. Risk factors for the development of toxicity include advanced age, depressed renal function, acid-base abnormalities, hypo- and hyperkalemia, hypomagnesemia, hypercalcemia, and concurrent use of other drugs that affect the pharmacokinetics of digoxin, such as quinidine, verapamil, and amiodarone.

The first step in successful treatment of digoxin toxicity is early recognition. Once toxicity is suspected, a careful history regarding dosage and frequency of digoxin use should be obtained. Laboratory tests, including serum creatinine concentration, digoxin serum level, and electrolyte levels, should be included in the initial evaluation. Cardiac monitoring should be performed in all patients with suspected toxicity. Both hypokalemia and hypomagnesemia should be corrected, with close monitoring to avoid excessive supplementation. Because of the extensive tissue distribution of digoxin, hemodialysis or hemoperfusion is generally ineffective for treatment of advanced toxicity and should be reserved for the patient with advanced renal dysfunction in whom acute digoxin intoxication may result in hyperkalemia.

Antiarrhythmic therapy may be considered in patients with hemodynamically compromising arrhythmias. Atropine is transiently effective in digoxin-induced bradyarrhythmias and can be used as a temporizing measure until more definitive therapy can be instituted. A temporary pacing wire should be used in patients with hemodynamically compromising bradyarrhythmias. Lidocaine and phenytoin have demonstrated efficacy in the treatment of digoxin-induced tachyarrhythmias. Both of these drugs have little effect on either sinus nodal or AV nodal tissue at therapeutic concentrations and therefore are least likely to potentiate any conduction disturbances associated with toxicity.

The preferred therapy for digoxin toxicity is digoxin-specific antibodies (Fab antibody fragments). The Fab antibody fragments bind to digoxin and the antibody fragment–digoxin complex is rapidly cleared. The use of digoxin-specific Fab antibodies is associated with a partial or complete response in 74% to 90% of patients with digoxin toxicity. The response to therapy is rapid (mean time to initial response = 19 minutes) and associated with few significant side effects (0 to 8%). Frequent monitoring of serum electrolytes, particularly potassium, is required, as administration of these antibody fragments frequently leads to significant hypokalemia. Widespread use of this therapy has been limited by its relative high cost; however, given its efficacy and short onset of action, the use of Fab antibody fragments may prove to be the most cost-effective way to manage patients with serious digoxin toxicity.

Digoxin-specific antibodies should be used in patients with clear evidence of toxicity and hemodynamically compromising arrhythmias. Ingestion of large quantities of digoxin (> 3 mg) associated with marked elevation in serum digoxin levels (≥ 5 ng/mL) warrants treatment with digoxin-specific antibodies even before arrhythmias develop.

ELECTROLYTE DISTURBANCES

Electrolyte abnormalities are an infrequent cause of bradyarrhythmias and, when present, are usually related to abnormalities in serum potassium concentration. *Hyperkalemia* raises the resting membrane potential in cardiac cells, which results in inactivation of ion channels responsible for impulse conduction. Sinus exit block, atrial quiescence, and high-degree AV block can result from significant elevation of the serum potassium concentration. Severe hyperkalemia can also lead to a slow, wide complex rhythm (Figure 33.8).

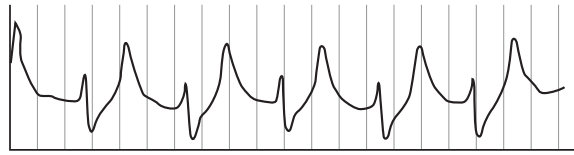


Figure 33.8 Hyperkalemia. Note characteristic loss of atrial activity (absent P waves), peaked T wave, loss of ST segment, and QRS widening.

Hypokalemia may promote atrial and ventricular premature depolarizations and atrioventricular conduction disturbances. Hypocalcemia by itself does not usually result in significant arrhythmias but may exacerbate conduction disturbances seen with hyperkalemia. Cardiac conduction can be depressed in severe hypermagnesemia, but respiratory depression usually occurs first at lower serum levels and therefore typically dominates the clinical picture.

HEART BLOCK DURING CATHETER PLACEMENT

During bedside catheter placement, it is not uncommon that a wire being placed during access may traverse the tricuspid valve and enter the right ventricle. This is particularly true during pulmonary artery catheterization when the goal is to advance the catheter through the right ventricle into the pulmonary artery. When a catheter or wire enters the right ventricle, it is possible for right bundle branch block (RBBB) to occur because of local trauma to the right bundle. The RBBB is usually transient and asymptomatic but may be seen in as many as 6% of patients who undergo pulmonary artery catheterization.

The development of RBBB is a concern whenever there is preexisting left bundle branch block (LBBB) and the patient develops complete heart block during catheter placement. However, the overall risk of complete heart block in one study by Shah et al was only shown to be 0.8% (1/113 patients). Another study showed complete heart block in only 2/47 patients with preexisting LBBB, and in both patients heart block occurred at least 1 day after catheter placement rather than during the actual procedure.

Thus, the risk of complete heart block in performing bedside catheter placement in patients with preexisting LBBB is low. However, the potential for complete heart block should be recognized, and having the ability to transcutaneously pace with a bedside defibrillator is recommended. The duration of complete heart block relates directly to the amount of time needed for conduction through the right bundle to return, which can vary substantially among patients. Placement of a transvenous pacing wire prophylactically, however, is not indicated given that the risk of placement likely exceeds its potential benefit given the rarity of occurrence. If RBBB occurs during catheter placement, it does not necessarily portend a greater likelihood for the patient to develop complete heart block in the future given that the conduction abnormality is iatrogenic and related to mechanical trauma, which should fully resolve.

Heart Transplant

Patients who have had a prior heart transplant represent a unique population when it comes to assessing incident bradyarrhythmias. Immediately after heart transplant, patients are typically tachycardic. However, because of extensive manipulation during surgery of the atria, age of the donor heart, or the duration of ischemic time for the explanted donor heart prior to reimplantation into the recipient, effective sinus node dysfunction may occur. In such situations, the heart rate, although in the "normal" range of 60 to 80 beats per minute, is nevertheless too slow for the patient's physiologic needs. These issues may or may not resolve with time, and patients may have

atrial epicardial pacing wires to maintain a higher heart rate. Most patients regain normal sinus node automaticity. However, if the patient continues to need pacing after a 7- to 10-day follow-up period, it is reasonable to place a single chamber atrial pacemaker if the patient has normal AV conduction.

In patients presenting with the new onset of bradyarrhythmias, whether disorders of sinus node function or AV conduction, it is reasonable to evaluate for rejection via a right ventricular biopsy. Patients late after heart transplant may also develop a transplant vasculopathy and rarely acute coronary occlusions that may present as bradyarrhythmias in the absence of chest pain resulting from the effective denervation of the heart. However, the occurrence of new pathologic bradyarrhythmias in patients with prior heart transplant should never be considered normal and requires workup for underlying causes.

Treatment

The treatment of the patient presenting with a bradyarrhythmia requires a structured assessment of the clinical relevance and mechanism of the arrhythmia as stated previously. Generally, the role of acute treatment involves consideration of (1) whether or not there are symptoms, (2) the degree of symptoms and hemodynamic compromise to determine the urgency of intervention, (3) whether there is a reversible cause, and (4) how long the patient's heart rate may need support between when the underlying cause may be reversed (if reversible) and when the return of conduction is expected. The best option for initial treatment depends on the equipment available and the experience of the clinician in offering specific therapies, as discussed next.

ACUTE MANAGEMENT

Bradycardia causing significant symptoms (altered consciousness, syncope, dizziness, lightheadedness) or significant hemodynamic compromise requires acute therapy, regardless of the cause. Early cardiovascular consultation can be helpful for acute and chronic management decisions in acutely symptomatic patients, in patients for whom reversible causes cannot be identified, and in those with preexisting heart disease.

The approach to the patient with acutely symptomatic bradycardia should follow the standard advanced cardiac life support (ACLS) guidelines (see Appendix D). Atropine (up to 3 mg IV) may be efficacious in treating any bradyarrhythmia that is associated with inappropriately high vagal tone. The decision to use atropine in patients with infranodal block should be made with care, however, given that atropine may paradoxically worsen the degree of AV block as the sinus rate increases (e.g., 2:1 block may become 3:1 or 4:1).

Transcutaneous pacing using pads placed in an anteroposterior (or less desirably an anterolateral) position can be effective in the acute management of patients with bradycardia leading to significant symptoms or hemodynamic compromise. Two large surface electrode pads are typically placed over the cardiac apex on the anterior chest wall and over the right posterior scapula. The output of the bedside defibrillator system is increased until reliable ventricular capture is achieved. However, because of the intervening skin, subcutaneous fat, muscle, and visceral structures, high outputs are often required for reliable capture, particularly in larger patients. Furthermore, consistent ventricular capture is unpredictable, often difficult to achieve, and associated with significant discomfort in the conscious patient. Thus, transcutaneous pacing should be used as a temporizing measure only. Furthermore, consideration to sedating the patient should be made. To ensure that the pacing pads are causing myocardial depolarization, assessment of the pulse via either the radial or femoral pulse should be made. Use of telemetry to evaluate for pacemaker capture is insufficient due to the large artifact that may impair evaluation for ventricular capture. Inconsistent or no capture may be seen in as many as 30% to 40% of patients with transcutaneous pacing.

Isoproterenol can be used to increase the heart rate temporarily in patients as well. Isoproterenol is a pure beta-adrenergic agonist with predominantly chronotropic cardiac effects. However, high doses of isoproterenol can precipitate tachyarrhythmias, both supraventricular and ventricular. It can also result in ischemia in patients with preexisting heart disease and should be used with extreme caution in this population, if at all. Furthermore, high doses of isoproterenol may lead to hypotension resulting in the need for the addition of pressors to support the heart rate.

Other medications that may be useful include scopolamine, disopyramide, and theophylline, which can act as either vagolytic or sympathomimetic agents in patients with sinus node dysfunction. However, these medications do not always work.

Any clinically symptomatic bradyarrhythmia that is not acutely reversible with medications or transcutaneous pacing mandates placement of a temporary transvenous pacing catheter. These catheters are introduced transvenously—preferably through the right jugular, left subclavian, or left brachial vein—and positioned in the right ventricular apex. An experienced operator should place these catheters, as this procedure is associated with significant risks, including vascular injury, cardiac perforation and tamponade, ventricular tachycardia, thrombosis, bleeding, and infection.

Some Swan-Ganz (pulmonary artery flotation) catheters have a port through which a pacing catheter can be passed into the right ventricle. There are two types of transvenous pacing wires including balloon-tipped and stiff-tipped wires. Balloon-tipped pacing wires decrease the risk of cardiac perforation, especially when being placed at the bedside without fluoroscopy support. However, stiff-tipped temporary pacing wires generally are more stable. In some patients it may be difficult to adequately position the pacing catheter at the right ventricular apex, and catheter migration with patient movement is an issue that needs to be recognized as either total or intermittent loss of capture on telemetry. Assessment of a ventricular threshold (i.e., the minimum electrical output required to consistently capture ventricular muscle leading to ventricular depolarization) should be assessed daily while patients have transvenous wires.

A permanent pacemaker wire placed under fluoroscopy and screwed into cardiac muscle using an active fixation mechanism offers an option in patients who require longer-term pacing needs but who are not candidates for a permanent pacemaker yet because of comorbidities such as infection. These wires must be placed in the electrophysiology laboratory and are generally introduced via the subclavian or internal jugular vein through a sheath, advanced to the heart under fluoroscopy, actively fixed to the right ventricular apex, and then sutured to the skin. Using an adapter, they may be attached to the same temporary pacing box used for temporary transvenous pacing wires. Permanent pacemaker wires are generally stable and may be left in place for as long as necessary until the patient's pacing needs have resolved or until a permanent pacemaker may be safely placed.

Chronic Management

The primary treatment option for chronic symptomatic bradycardia is permanent pacemaker implantation. Whether or not permanent pacing is indicated may be the subject of considerable debate, mostly because of the difficulty in providing a secure definition of *symptomatic* bradycardia and in turn attributing a patient's specific symptoms to the bradyarrhythmia. Clinically relevant manifestations of the low cardiac output state may be fairly vague, particularly in the elderly patient. Occasionally, mild personality changes or signs of apparent dementia are the only clues to the need for intervention, and the benefit of a pacemaker may be recognized only after placement.

In the ICU, the typical indications for permanent pacing are similar to those discussed for temporary pacing interventions. Disorders resulting in symptomatic bradycardia that are not transient in nature or due to a reversible cause are appropriately treated with pacemaker implantation. As noted earlier, these disorders are caused by either sinus node dysfunction or disorders of AV

conduction. In addition, pacing is also considered for asymptomatic patients at high risk for the development of complete heart block (such as patients with new bifascicular block in the setting of myocardial infarction [Chapter 50]) or patients with symptomatic bradycardia caused by medications that are required to treat other conditions. Guidelines published in 2008 from the American College of Cardiology and American Heart Association discuss the indications for permanent pacemaker implantation and whether implantation is indicated (class I), suggested (class IIa), reasonable (class IIb), or unnecessary (class III).

Before permanent pacemaker implantation, it is extremely important to exclude active infection. The risk of infection in a population of ICU patients may be considerable. Pacemaker infection usually cannot be resolved by antibiotic therapy alone and requires removal of both the generator and the intracardiac lead system. In situations in which pacing is required but ongoing infection is a concern, as in the ICU, temporary transvenous pacing as described previously using either an externalized permanent pacing wire or a temporary transvenous wire should be employed until permanent implantation can be performed safely.

PACEMAKER TROUBLESHOOTING

Modern permanent pacemakers are extremely reliable. However, pacemaker malfunction, relating to either failure to pace (capture) or failure to sense does occasionally occur. Causes of transient or sustained pacemaker malfunction include the following: (1) lead fracture or migration, (2) generator battery depletion, and (3) improper programming. In addition, apparent malfunction can often be explained by appropriate programmable behaviors (hysteresis, safety pacing, pacing options that are used to promote intrinsic conduction) that may be different in devices manufactured by different vendors. Because of the complexity involved, cardiology consultation should be obtained to evaluate suspected pacemaker malfunction.

One important bedside intervention that can be rapidly employed for pacing malfunction is applying a magnet. Applying a magnet over the top of pacemaker generators causes suspension of sensing function, resulting in single- or dual-chamber asynchronous pacing. This can be helpful when the ventricular rate is inappropriately slow because of oversensing by the pacemaker of nonventricular signals resulting in inhibition of pacing.

However, an important consideration is that implantable cardioverter defibrillators, which also have pacing functions, do not respond in the same way to magnet application. Specifically, magnet application results in inhibition of therapies for ventricular tachyarrhythmias but does not switch the device to an asynchronous pacing mode. In these patients, conversion to an asynchronous mode must be done using a device programmer. Applying a magnet in patients with devices also requires one to be certain that the magnet is directly over the device, which may not be trivial in obese patients in whom the location of the device may not be readily apparent.

Electromagnetic interference from other technology in the hospital setting may also result in transient or permanent device malfunction. Most technological devices, including cell phones, telemetry, and the like, have not been demonstrated to result in significant interference with normal pacemaker or defibrillator function. However, both computed tomography scans and magnetic resonance imaging have been reported to cause electromagnetic interference with implantable cardiac devices. The risk is low though. Computed tomography scans may typically be performed without significant concern for pacemaker malfunction. However, although magnetic resonance imaging scans are being performed with electrophysiology support in more institutions, close device follow-up before and after the scan is still required. Sometimes, a cause of transient electromagnetic interference may not be readily identified but only manifests as a transient episode of failure to sense or failure to capture on telemetry. In these cases, electrophysiologic consultation may be required to determine whether revising the device (i.e., implanting new leads or a new generator) may be required.

Summary

The care of the patient presenting with a bradyarrhythmia in the ICU setting may be complex. Approach to these patients requires a structured consideration for (1) the clinical relevance of the low heart rate; (2) the cause of the bradyarrhythmia and whether or not the cause is reversible; (3) the attributable risk both acutely and chronically; (4) the best intervention—whether pharmacologic, using transcutaneous pads, or placing intracardiac pacing wires—depending on the rapidity with which therapy needs to be initiated and the availability of appropriate expertise and equipment; and (5) whether or not a permanent pacemaker is indicated and the appropriate timing of implantation. Many of these considerations, particularly the reversibility of the underlying cause and the clinical relevance of the arrhythmia, may not be readily apparent within even the first several days of patient presentation, and the situation thus requires close collaboration between the primary team and cardiovascular consultants to accurately determine therapeutic needs.

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CHAPTER 34

Arrhythmias (Tachycardias)

Gregory E. Supple ■ Francis E. Marchlinski

Management of tachyarrhythmias in the intensive care unit (ICU) requires a systematic approach to evaluation, electrocardiographic (ECG) diagnosis, and treatment. Whereas some tachycardias are transient in nature, a result of drug toxicity or electrolyte imbalance, others require further cardiac evaluation and long-term management. This chapter presents a general approach to the evaluation of the ICU patient with a tachyarrhythmia, reviews the differential diagnosis, describes ECG clues for both narrow and wide complex tachycardias, and details options related to acute treatment. Specific clinical situations are also described, such as digoxin toxicity, ventricular tachycardia (VT) in the absence of structural heart disease, the Wolff-Parkinson-White (WPW) syndrome, and acute management of the patient with an implantable cardioverter-defibrillator (ICD).

General Approach to Tachyarrhythmias in the ICU Setting

OVERVIEW

Recommendations for acute treatment can come only after a rapid but accurate assessment of the arrhythmia, its consequences, and its potential causes (Box 34.1). Whereas the hemodynamic consequences of the tachycardia dictate the urgency of treatment, timely assessment of multiple other factors is also essential.

Most tachyarrhythmias in the ICU setting are precipitated or potentiated by metabolic and hemodynamic derangements, electrolyte imbalances, or drug effects. These include sinus tachycardia, atrial fibrillation, atrial flutter, multifocal atrial tachycardia, automatic atrial and junctional tachycardias, and polymorphic VT. In contrast, sustained monomorphic VT, atrioventricular (AV) nodal reentrant tachycardia (AVNRT), reentrant atrial tachycardia, and atrioventricular reentrant tachycardia (AVRT)—which uses the atria, AV nodal tissue, ventricles, and an accessory pathway—occur in the setting of a predisposing structural substrate. Even with such a substrate, however, a metabolic or hemodynamic factor may be responsible for the initiation and maintenance of the tachycardia. Furthermore, reversal of these underlying abnormalities may control the tachycardia and prevent its recurrence despite the presence of a substrate abnormality.

DIAGNOSTIC TOOLS

The appropriate intervention for a tachyarrhythmia depends on obtaining adequate information to arrive at the correct ECG diagnosis (Table 34.1). A reference or baseline 12-lead ECG during sinus rhythm should be sought immediately. This may provide important information regarding underlying heart disease, conduction abnormalities, and baseline P wave morphology. A 12-lead

Additional online-only material indicated by icon.

BOX 34.1 ■ Checklist for Rapidly Assessing Patients with Tachyarrhythmias

1. Hemodynamic status: perform emergency cardioversion if unstable ("When in doubt, knock it out"; see text)
2. Cardiac status: check for angina and heart failure symptoms
3. Volume status: consider hypovolemia, blood loss, or volume overload
4. Body temperature: evaluate for fever or hypothermia
5. Medications: note both dosage and time of administration, especially:
   - Theophylline
   - Catecholamine infusions
   - Digoxin
   - Antiarrhythmic agents
6. Serum electrolyte levels: especially K^+, Mg^{2+}, and Ca^{2+}
7. Oxygen saturation and hemoglobin level
8. Acid-base balance
9. Pain control status

TABLE 34.1 ■ **Differential Diagnosis of Sustained Supraventricular Tachycardia***

Rhythm (Figure Number)	Key Features	Response to Adenosine or Vagal Maneuver
Sinus tachycardia (34.2*A*)	Upright P wave in II, III, aVF; inverted P wave in aVR	No effect or transient slowing
Atrial fibrillation (34.2*B*)	No repetitive organized atrial activity; irregularly irregular ventricular response	Transient slowing of ventricular response
Atrial flutter (34.2*C*)	P wave activity 260–300 beats per minute; ventricular response 2:1, but higher-grade AV block possible	Transient slowing of ventricular response with unmasking of flutter waves (see Figure 34.1)
Multifocal atrial tachycardia (34.2*D*)	Multiple (≥ 3) discrete P wave morphologies with isoelectric interval between P waves	No effect or transient AV block
Atrial tachycardia (34.2*E*)	P wave morphology distinct from sinus P wave; may have variable AV block	Transient AV block; termination of tachycardia is possible
Atrial tachycardia of digoxin toxicity	Upright P wave in II, III, aVF, V_1; typically with variable AV block and ventriculophasic effect	Transient AV block
Junctional tachycardia of digoxin toxicity	Regular RR interval; no association between P wave and QRS complex	No effect
AV nodal reentrant tachycardia (34.2*F*)	P wave may only be visible at the end of the QRS complex (pseudo R wave in V_1; pseudo S wave in II, III, aVF)	Termination of tachycardia
AV reentrant tachycardia (34.2*G*)	P wave is seen after the QRS complex; inverted P wave in II, III, aVF	Termination of tachycardia after the P wave

*Ranked in order of frequency of occurrence in ICU patients.
AV, atrioventricular.

ECG during the tachycardia provides further information regarding the AV relationship during tachycardia, morphologic features of the QRS complex, and P wave morphology. Long telemetry rhythm strips are also helpful in determining the AV relationship, regularity of the ventricular response, and initiation and termination of the tachycardia (Table 34.2). Additional information regarding the AV relationship may be obtained by recording directly from epicardial pacing leads in the postoperative cardiac patient or from permanent endocardial pacing leads.

Many tachycardias are short-lived or require immediate cardioversion, making it difficult to obtain a 12-lead ECG during the event. In these cases, telemetry recordings from the appropriate leads are crucial. The V_1 precordial lead is the most helpful lead in assessing bundle branch block (BBB) morphology and suspected VT. Based on morphologic criteria, V_1 may also be useful in localizing the arrhythmia and guiding pharmacologic and ablative treatment. It is important to note that V_1 and MCL_1 (modified chest lead 1—the bipolar telemetry vector of left arm negative and right chest wall positive) recordings are not equivalent. Although the two leads may appear identical during sinus rhythm, they may be very different during wide complex tachycardias.

As a rule, the inferior limb leads (II, III, aVF) are good starting points for supraventricular tachycardias because P waves and atrial flutter waves are often well seen in these leads. If the telemetry system allows simultaneous monitoring of two leads, V_1 and an inferior limb lead provide the greatest amount of information. If only one lead can be monitored at a time, lead selection should be based on the arrhythmic information sought for an individual patient.

Interventions during tachycardia can also provide useful information. Slowing AV nodal conduction with vagal maneuvers or pharmacologic agents can reveal previously masked flutter waves or the P waves of atrial tachycardia (Figure 34.1). Adenosine, an endogenous nucleoside, interacts with specific receptors on the extracellular membrane acutely slowing AV conduction.

TABLE 34.2 ■ **Electrocardiographic Clues from Initiation and Termination of Supraventricular Tachycardias**

Rhythm	Initiation Phase	Termination Phase
Sinus tachycardia	"Warm-up" in atrial rate	Atrial rate slows gradually without an abrupt stop
Atrial flutter	Transient AV block may reveal flutter waves (see Figure 34.1)	
Atrial tachycardia	Acute change in rate, followed by warm-up in atrial rate with changing PR interval; transient degree of AV block during which P waves appear	Oscillations in PP interval precede changes in RR interval; terminates after QRS complex
Junctional tachycardia	No APC triggering the tachycardia	
AV nodal reentrant tachycardia	APC followed by a significantly prolonged PR interval and then supraventricular tachycardia; BBB only transient following initiation	Terminates after P wave with adenosine
AV reentrant tachycardia	APC and slightly prolonged PR interval; late coupled VPC; persistent BBB; fixed RP relationship	Oscillations in RR interval precede changes in PP interval; terminates after P wave with adenosine; may terminate after a single, especially late coupled, VPC

AV, atrioventricular; APC, atrial premature contraction; BBB, bundle branch block; VPC, ventricular premature contraction.



Figure 34.1 **A,** Regular supraventricular tachycardia at a rate of 150 beats/min. **B,** Pharmacologic slowing of atrioventricular (AV) nodal conduction results in variable AV block suggesting atrial flutter. **C,** After slowing conduction through AV node even more, the P waves of atrial flutter (conducted at 4:1) become clearly evident *(arrows)*.

Because adenosine has a half-life of only 0.5 to 5 seconds, doses (6 mg and then 12 mg) must be given in a rapid IV bolus injection followed by a flush. Even administration through a peripheral intravenous line can attenuate its effects. The short-lived adverse effects of adenosine include facial flushing, chest pain or pressure, bronchospasm, and dyspnea. By briefly but effectively blocking the AV node, adenosine is capable of terminating AVNRTs. Adenosine is not a perfect diagnostic tool, however, because it may also terminate some episodes of focal triggered atrial tachycardia and VT.

THE "WHEN IN DOUBT, KNOCK IT OUT" RULE

Severe hemodynamic instability resulting from a tachycardia warrants prompt electrical cardioversion. Before cardioversion, however, one needs to consider that the tachycardia may be sinus tachycardia or multifocal atrial tachycardia, neither of which responds to electrical cardioversion. In addition, the hemodynamic instability may be due to a separate cause, such as blood loss or sepsis, and the tachyarrhythmia is just a secondary event. Once the decision is made to perform electrical cardioversion, patient comfort should be ensured by administering a short-acting IV benzodiazepine, such as midazolam, or the anesthetic agent propofol (see Chapter 5).

One must choose a mode of delivery (synchronous or asynchronous) and an energy level. Delivery of shock energy for ventricular fibrillation (VF) and polymorphic VT should be

performed in the asynchronous mode. For all other arrhythmias, energy should be delivered in the synchronous mode to decrease the risk of causing arrhythmia degeneration or VF. For any rhythm with dire hemodynamic consequences, energy output should begin at 200 joules and then should be increased to 300 joules or the maximum available dose from the defibrillator if the initial attempts fail (see Appendix D for Advanced Cardiac Life Support [ACLS] algorithms). Only in the stable patient should lower energy levels be attempted.

One always should anticipate adverse consequences when performing electrical cardioversion or defibrillation. Even in the stable patient, synchronous cardioversion can precipitate VF. Because bradycardia and significant sinus pauses are not unusual after cardioversion, IV atropine should always be immediately available, and ready access to an external pacing unit is desirable.

Narrow Complex Tachycardias

Supraventricular tachycardia (SVT) is a commonly used but imprecise term. By definition, all narrow complex tachycardias, including sinus tachycardia, are supraventricular in origin because only depolarization over the His-Purkinje system results in a narrow QRS. The frequency of the different SVTs occurring in the ICU setting differs from that seen in the emergency department or outpatient office (Figure 34.2 and see Table 34.1). Underlying diseases, heightened sympathetic tone, and use of medications, such as inotropes, theophylline, or digoxin, can precipitate these tachyarrhythmias. Clues to their ECG diagnosis can be found in rhythm strip analysis with recording of the onset and termination of tachycardia (see Table 34.2). More detailed recommendations of pharmacologic and nonpharmacologic management strategies for specific SVTs are discussed next.

SINUS TACHYCARDIA

The most common SVT encountered in the ICU is sinus tachycardia, which occurs in response to underlying conditions such as pain, fever, infection, anemia, pulmonary embolism, thyrotoxicosis, myocardial ischemia, and congestive heart failure (CHF) (see Figure 34.2*A*). Autonomic dysfunction may also play a role, particularly in certain neurologic disorders, such as Guillain-Barré syndrome. The clinical challenge lies in making the diagnosis of sinus tachycardia and recognizing its significance as a secondary problem. It should be viewed as a warning sign of underlying abnormalities and prompt a thorough evaluation. Treatment is directed toward the underlying cause.

ATRIAL FIBRILLATION AND ATRIAL FLUTTER

Atrial fibrillation and atrial flutter are similar arrhythmias that occur commonly in the ICU (see Figure 34.2*B* and *C*). Risk factors for the development of atrial fibrillation include advanced age, CHF and valvular heart disease, systemic hypertension, pulmonary disease, sleep apnea, and thyrotoxicosis. Acute respiratory failure and high sympathetic tone, particularly in patients with other risk factors, can precipitate a paroxysm of atrial fibrillation or flutter. On the 12-lead ECG, atrial fibrillation is marked by the replacement of organized atrial activity with an irregular undulating baseline of variable amplitude. At times, the undulations may be coarse and mimic atrial activity; however, these coarse waves are not truly cyclical: the RR interval is always irregular and characteristically some will occur < 200 msec apart.

In contrast, atrial flutter is due to a reentrant mechanism within the atria and results in regular flutter waves (typically at a rate of 240 to 300 beats per minute [bpm]) on the 12-lead ECG. In the absence of medications, the ventricular rate is typically regular, with 2:1 conduction of flutter waves, resulting in a typical regular ventricular rate of 130 to 150 bpm. In fact, when encountering a regular, narrow complex tachycardia at the rate of 130 to 150 bpm, one should always first consider

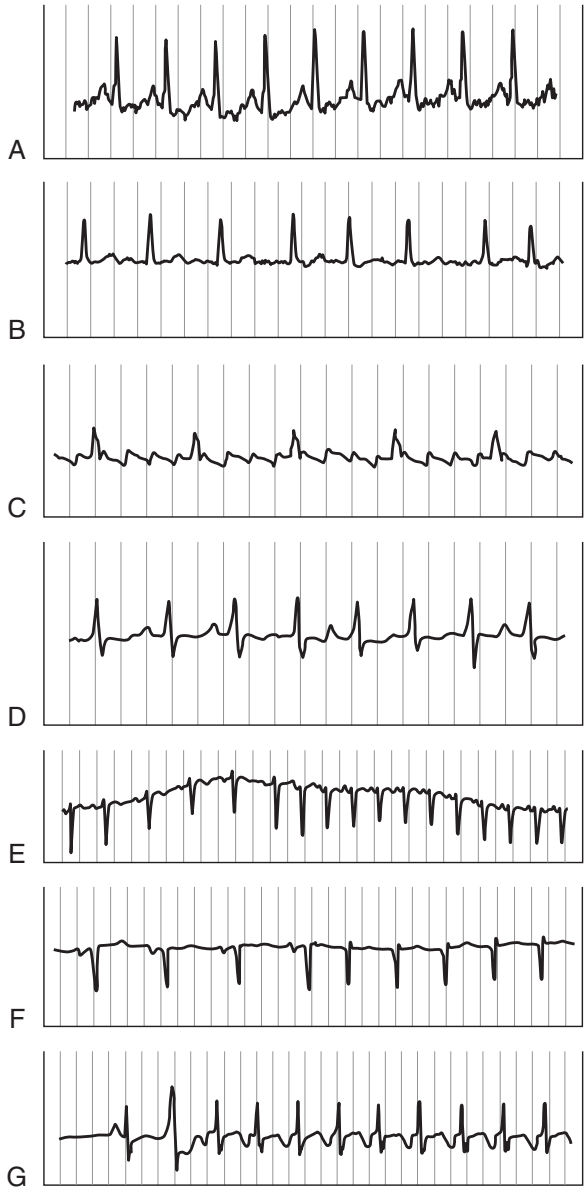


Figure 34.2 **A,** Sinus tachycardia. **B,** Atrial fibrillation. **C,** Atrial flutter. **D,** Multifocal atrial tachycardia. **E,** Atrial tachycardia. **F,** Atrioventricular nodal reentrant tachycardia (AVNRT). **G,** Atrioventricular reentrant tachycardia (AVRT). See Tables 31.2, 34.1, 34.2, and 31.3 and the text for diagnostic features of each tachycardia.

the diagnosis of atrial flutter. It is frequently more difficult to control the ventricular rate in atrial flutter than in atrial fibrillation because of the slower and more organized impulses reaching the AV node. Flutter waves can be easily overlooked, and blocking conduction in the AV node can help unmask them (see Figure 34.1). If atrial wires/leads (temporary or permanent) are present, direct recordings from these wires can help clarify the diagnosis.

TABLE 34.3 ■ **Treatment of Atrial Fibrillation and Flutter: Ventricular Rate Control**

Medication	Administration*	Advantages	Disadvantages
Propranolol	IV bolus or oral	Shorter half-life, especially effective for thyrotoxicosis	Frequent dosing required for control
Metoprolol	IV bolus or oral	Longer half-life	
Esmolol	IV infusion	Half-life of 9 minutes	Needs close monitoring
Verapamil	IV bolus or infusion or oral		Acute control lasts only 30 minutes after IV dose; negative inotrope
Diltiazem	IV bolus or infusion or oral	Short half-life	Less negative inotropic effects than verapamil
Digoxin	IV bolus or oral	Positive inotropic effect	Delayed onset of action Narrow therapeutic window

*For specific doses of digoxin based on renal function, see Table 17.2, Chapter 17.

Acutely, these arrhythmias can result in a rapid ventricular rate, loss of effective atrial contraction, and hypotension. In this situation, the treatment is electrical cardioversion. If the patient is stable, management is directed at controlling the ventricular rate, converting the arrhythmia to sinus rhythm, maintaining sinus rhythm, and preventing embolic sequelae.

A number of pharmacologic agents are available to control the ventricular response during atrial fibrillation and flutter (Table 34.3). Once the rate is controlled and the patient is hemodynamically stable, cardioversion to sinus rhythm can be pursued on an elective basis. The timing of elective cardioversion is largely determined by the need to reduce the risk of thromboembolic complications. The lack of organized atrial activity associated with atrial fibrillation leads to circulatory stasis within the atria and can result in formation of atrial thrombi and embolism into the systemic circulation. Even in new-onset atrial fibrillation, there is some embolic risk. If a patient has no contraindications, anticoagulation should be started as soon as possible, certainly within 24 to 48 hours if spontaneous conversion to sinus rhythm has not occurred. If a patient cannot receive anticoagulation, prompt cardioversion within 24 to 48 hours should be considered. In addition, patients with known risk factors for stroke who are in atrial fibrillation for over 24 hours may require a transesophageal echocardiogram to exclude the presence of a thrombus in the left atrial appendage before cardioversion.

When the duration of atrial fibrillation is unclear, one must assume that it has been present for > 48 hours. In this case, conventional therapy has consisted of anticoagulation for 4 to 6 weeks before cardioversion. A transesophageal echocardiogram can be used to rule out the presence of thrombus located in the left atrial appendage, but the absence of thrombus does not preclude the need for immediate postcardioversion heparin therapy and anticoagulation for several weeks thereafter. Anticoagulation is essential during this period because atrial stunning from intracellular calcium accumulation during atrial fibrillation may lead to thrombus formation despite restoration of sinus rhythm. Atrial stunning is a persistent mechanical atrial dysfunction despite restored bioelectric function and can take 4 to 6 weeks to resolve. Patients with atrial flutter are at a similar risk for embolic phenomena as those with atrial fibrillation and should also receive anticoagulation.

Once the decision is made to proceed to cardioversion, several options exist, particularly for atrial flutter. Because atrial flutter is a reentrant arrhythmia, overdrive pacing by means of a permanent or temporary pacing wire or an esophageal electrode can terminate the tachycardia. Overdrive pacing, however, can result in atrial fibrillation rather than sinus rhythm.

Atrial fibrillation and flutter respond to the same antiarrhythmic drugs outlined in Table 34.4. In fact, atrial fibrillation frequently organizes into stable atrial flutter on these medications. It is common, however, for these arrhythmias to resist pharmacologic interventions and require electrical cardioversion. Despite this, the use of antiarrhythmic agents before electrical cardioversion is indicated because drug treatment may help maintain sinus rhythm after cardioversion. In patients whose condition is stable, electrical cardioversion of atrial fibrillation typically begins at 200 joules, but higher doses of energy may be required. It is always performed in the QRS synchronous mode. Cardioversion of atrial flutter generally requires significantly lower energies, usually 50 to 100 joules, and again should always be delivered in the synchronous mode. An amnestic agent, such as midazolam, should always be given beforehand.

Some patients have a clear precipitating factor for atrial fibrillation, such as pulmonary embolism or pneumonia, and do not require long-term medical management. Spontaneous conversion to sinus rhythm may occur as the patient recovers from the acute insult. Other patients who have underlying risk factors remain at risk for recurrence and may require chronic

TABLE 34.4 ■ **Treatment of Atrial Fibrillation and Flutter: Conversion to Sinus Rhythm**

Medication	Administration	Advantages	Disadvantages
Procainamide	IV bolus and infusion or oral	IV bolus usually tolerated; first choice for medical treatment of atrial fibrillation over a bypass tract (see text)	Hypotension with IV; long-term use limited by side effects; proarrhythmia
Quinidine	IV bolus or infusion or oral	No negative inotropic effects	Proarrhythmia; vagolytic effect may cause increase in heart rate; hypotension with IV; gastrointestinal side effects common
Disopyramide*	Oral	Twice-a-day dosing	Anticholinergic effect; negative inotropic effect
Flecainide*	Oral	Twice-a-day dosing	Proarrhythmia, especially in congestive heart failure and coronary artery disease; negative inotropic effect; teratogenic
Propafenone*	Oral	Beta-blocking adds to rate control	Negative inotropic effect
Sotalol*	Oral	Beta-blocking adds to rate control	Proarrhythmia; negative inotropic effect
Amiodarone	IV or oral	More effective in maintaining sinus rhythm; once-daily dosing; long half-life (2–15 weeks) after prolonged therapy	Variety of side effects, most reversible; rare but potentially fatal lung fibrosis with long-term administration
Dronedarone*	Oral	Derivative of amiodarone without the iodine moiety and fewer long-term side effects; shorter half-life	Not as effective as amiodarone; contraindicated in patients with advanced or decompensated heart failure

*Consider cardiology consultation before using these agents.

antiarrhythmic management and anticoagulation. The patient with atrial fibrillation and the WPW syndrome is discussed later.

MULTIFOCAL ATRIAL TACHYCARDIA

Multifocal atrial tachycardia (MAT) (see Figure 34.2*D*), also referred to as chaotic atrial tachycardia, occurs exclusively in the setting of a serious underlying disease, typically a chronic obstructive pulmonary disease (COPD) flare, other types of acute respiratory decompensation, pulmonary embolism, or CHF. The presence of MAT has been associated with a high in-hospital mortality rate, which correlates with the severity of the underlying disease rather than with the hemodynamic consequences of the tachycardia. The atrial rate in MAT tends to be 100 to 150 bpm but can be higher. The ECG reveals at least three P wave morphologies with marked variation in the PP intervals and frequently the PR intervals (see Table 34.1).

The most effective treatment for MAT is treatment of the underlying condition and cessation of potentially exacerbating drugs, such as theophylline. Patients may have concomitant electrolyte disturbances such as hypokalemia and hypomagnesemia that exacerbate the arrhythmia, and magnesium administered intravenously has been reported to control MAT in such patients. In general, electrical cardioversion, class IA antiarrhythmic agents, and digoxin are ineffective. Occasionally, when the rate is very rapid, it becomes important to control the ventricular response. Calcium channel blockers and amiodarone have been used with variable success; the use of beta-blockers, even cardioselective agents, is often limited in these patients because of concomitant bronchospastic disease.

AV NODAL REENTRANT TACHYCARDIA

AV nodal reentrant tachycardia (see Figure 34.2*F*) is a common mechanism of SVT, although it occurs less often in the ICU than the tachycardias discussed earlier. AVNRT can occur at any age, is unrelated to preexistent heart disease, and depends only on the presence of two functionally dissociated AV nodal pathways. The reentry circuit also occurs within the AV node and results in near simultaneous depolarization of both the atrium and ventricle (see Table 34.1). The ECG may reveal a retrograde P wave (inverted P waves in the inferior leads [II, III, and aVF]) that generally occurs at the same time as the QRS complex making it difficult to discern—however, when compared to the QRS in sinus rhythm, a terminal negative deflection in lead II or III or a terminal positive deflection ("pseudo-R") in V1 is often appreciable (see Figure 34.2*F*). The tachycardia rate ranges from 120 to over 200 bpm with regular RR intervals. Hemodynamic consequences are due to increased heart rate and the loss of sequential AV contraction. Patients with normal left ventricular function generally tolerate it, but substantial hypotension can result. Treatment is directed at slowing conduction within the AV node, thereby terminating the tachycardia. Maneuvers that increase vagal tone, such as a Valsalva maneuver, gagging, and carotid sinus massage, are often effective. Likewise, drugs such as adenosine, calcium antagonists, and beta-blockers are useful. Despite its AV nodal blocking effects, digoxin is usually ineffective as acute therapy. A variety of agents, including calcium antagonists, beta-blockers, digoxin, and class IA and IC drugs, can all be used to prevent recurrences. Radiofrequency catheter ablation, a curative procedure, is the therapy of choice to prevent recurrent AVNRT in the symptomatic patient.

AV REENTRANT TACHYCARDIA OVER A BYPASS TRACT

AV reentrant tachycardia is an SVT that uses the AV node and bypass tract (also called an accessory pathway) as the two limbs of the reentrant pathway (Figure 34.2*G*). Like AVNRT, AVRT may occur at any age and is not associated with underlying heart disease. The baseline 12-lead ECG may reveal preexcitation over the bypass tract (Figure 34.3) or may be normal (a so-called concealed accessory

pathway). The AVRT circuit can result in (1) a narrow complex tachycardia when the AV node serves as the antegrade limb and the ventricle is depolarized over the His-Purkinje system or (2) a wide complex tachycardia when antegrade conduction occurs over the bypass tract. Because both the atrium and ventricle are necessary components to the circuit, a 1:1 AV relationship exists and retrograde P waves are often discernible on the 12-lead ECG (see Table 34.1). During a given tachycardia, the RP intervals remain constant, which can help differentiate it from an atrial tachycardia. The RP interval, however, depends on the individual characteristics of the bypass tract and can be short or long.

Treatment is directed at slowing conduction within the AV node, usually the most vulnerable limb of the circuit, which results in termination of the SVT. For acute termination of AVRT, vagal maneuvers may be effective. If not, adenosine is the drug of choice. This medication can rarely precipitate atrial fibrillation with rapid ventricular response over the accessory pathway or even VF; therefore, an external defibrillator should be readily available when administering these medications. If the patient has a surface ECG manifesting WPW syndrome during sinus rhythm and is predisposed to developing atrial fibrillation, IV verapamil should be avoided and procainamide is the preferred therapy (see "Atrial Fibrillation in Patients with Wolff-Parkinson-White Syndrome" below). For prevention of recurrent AVRT, antiarrhythmic agents such as flecainide or sotalol, which can slow conduction over the bypass tract, and calcium antagonists or beta-blockers, which slow conduction over the AV node, can be used, although radiofrequency catheter ablation is the most effective method.

OTHER ATRIAL TACHYCARDIAS

In the ICU setting, atrial tachycardia generally occurs in patients with underlying heart disease, COPD, pneumonia, pericarditis, or digitalis toxicity (see Figure 34.2*E*). Atrial rates are commonly 150 to 200 bpm with P wave morphology on the 12-lead ECG distinct from the sinus P

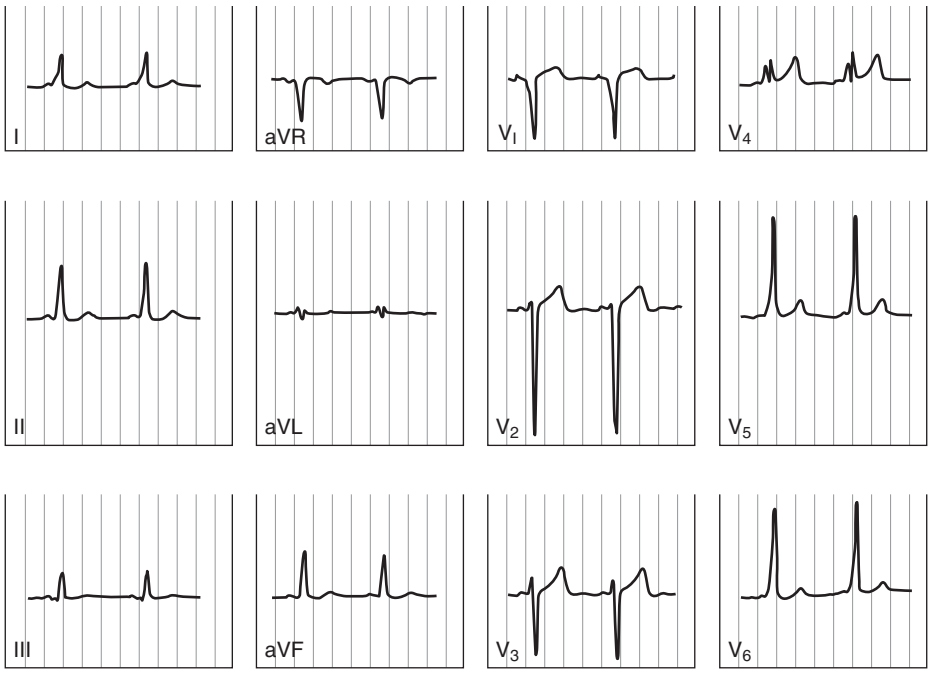


Figure 34.3 Normal sinus rhythm in a patient with Wolff-Parkinson-White syndrome. Note the short PR interval (< 0.12 sec) and slurred onset of QRS complexes, the hallmark of preexcitation.

wave (see Table 34.1). The ventricular response may be 1:1, 2:1, or variable AV conduction block, such as Wenckebach (Mobitz I) block.

Treatment of atrial tachycardia consists of ventricular rate control with AV nodal blocking agents and suppressive therapy with antiarrhythmic drugs. The tachycardia is often resistant to electrical cardioversion. Reversible underlying conditions, such as digitalis toxicity, pericarditis, or respiratory decompensation, should be aggressively treated if present. Otherwise, class IA agents such as procainamide or the class III agent amiodarone, administered intravenously, are appropriate in an ICU setting. Class IC agents, such as flecainide, or other class III agents, such as sotalol, can also be very effective but should be used with caution in patients with underlying cardiac disease.

ACCELERATED JUNCTIONAL RHYTHM

The AV junctional pacemaker typically fires at a rate of 40 to 60 bpm. Junctional tachycardia with rates above 100 bpm occurs in certain clinical situations such as digitalis intoxication, rheumatic fever, myocardial ischemia, and postoperatively after cardiac surgery, especially after valvular procedures. Atrial activity may be sinus P waves with AV dissociation or inverted P waves reflecting retrograde activation. Frequently, there is a 1:1 AV relationship. This differentiates it from the junctional tachycardia of digoxin toxicity, which has some degree of AV block or frank dissociation. In addition, an automatic junctional tachycardia often exhibits a fluctuating rate that can differentiate it from AVNRT. Loss of sequential AV contraction, especially in patients with poor left ventricular function, can have adverse hemodynamic effects. In the postoperative cardiac surgery patient, temporary atrial wires can often overdrive the rate of the junctional rhythm. Otherwise, management is supportive and directed toward the precipitating factor.

ATRIAL FIBRILLATION IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME

Patients with the WPW syndrome have accessory muscular connections between the atrium and ventricle, historically called Kent bundles, which are responsible for the preexcitation seen on the ECG. Typically, the ECG during normal sinus rhythm reveals a short PR interval (< 120 msec) and a wide QRS complex (> 120 msec) with a slurred upstroke (delta wave) (see Figure 34.3). These patients are predisposed to developing a number of SVTs, including atrial fibrillation. Because the ventricular response during atrial fibrillation can be rapid over the bypass tract with heart rates well over 200 bpm (Figure 34.4), these can degenerate into VF. If the patient's condition is hemodynamically unstable, immediate cardioversion should be performed.

Of note, standard AV nodal blocking regimens can actually increase the ventricular response in the patient with WPW syndrome and result in VF. For example, digoxin can directly increase the ventricular rate by accelerating antegrade conduction over the bypass tract. Verapamil can also

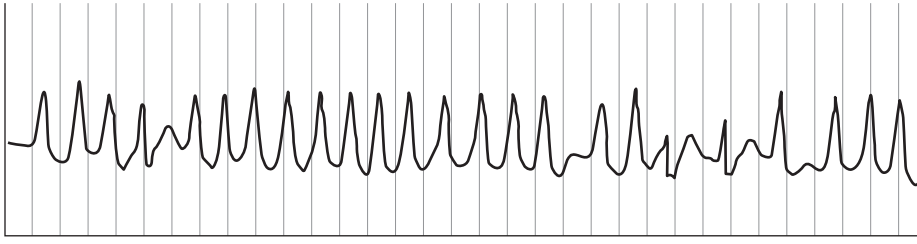


Figure 34.4 Atrial fibrillation in the same patient as shown in Figure 34.3. Note the irregularity of the RR intervals and the bizarre and changing morphologies of the QRS complexes. The shortest RR intervals occur at 300 beats per minute and could result in degeneration into ventricular fibrillation.

result in a faster ventricular response through vasodilatation and reflex sympathetic stimulation. Therefore, if the patient's condition is stable, conversion to sinus rhythm with procainamide or electrical cardioversion with adequate sedation is the treatment of choice.

Wide Complex Tachycardias

A wide complex tachycardia that is monomorphic—that is, all QRS morphologies are identical—can pose a diagnostic dilemma because a wide QRS complex may be due to VT or SVT with bundle branch block (BBB). The patient's hemodynamic response also cannot be used to differentiate between the two mechanisms: some patients with VT can be minimally symptomatic whereas some with SVT can have hemodynamic collapse. When the patient's condition is unstable, regardless of mechanism, he or she should be immediately cardioverted or defibrillated. If initial cardioversion or defibrillation is unsuccessful, repeated high-energy defibrillation should be delivered and cardiopulmonary resuscitation initiated. If the tachycardia remains refractory or VF occurs, standard therapy is recommended using high-energy shocks and amiodarone or lidocaine administration (see Appendix D for ACLS algorithms).

If the patient's condition is stable, however, a precise diagnosis should be pursued. VT carries a very different prognosis from SVT and requires different long-term management. Because the clinical scenario cannot definitively differentiate between diagnoses, ECG data are critical. Whenever possible, one should obtain a 12-lead ECG during the tachycardia to evaluate QRS morphology and the AV relationship (Box 34.2). The presence of AV dissociation (ventricular activity independent of atrial activity) is diagnostic of VT. Conducted sinus beats in the form of capture beats (QRS complex identical to baseline morphology) or fusion beats (distinct QRS morphology) also confirm the diagnosis of VT (Figure 34.5).

Morphologic features of the QRS complex are also important because they reflect how the ventricles have been activated. If the morphology is similar to the BBB pattern on the baseline sinus rhythm ECG or during times of rate-related BBB (e.g., during clear sinus tachycardia or an

BOX 34.2 ■ Electrocardiographic Support for Diagnosis of Ventricular Tachycardia

1. Atrioventricular dissociation
2. Right superior QRS axis in the frontal plane (positive in aVR and negative in I and aVF)
3. QRS duration > 140 msec in the absence of antiarrhythmic drug therapy
4. Evidence of Q wave myocardial infarction pattern on baseline ECG
5. Bundle branch block (BBB) pattern during wide complex tachycardia different from BBB pattern on baseline ECG
6. QRS complex narrows during tachycardia
7. Morphologic characteristics:
   a. RBBB tachycardia:
   (1) Duration of QRS onset to nadir of S wave in any precordial lead > 100 msec
   (2) Monophasic R or QR pattern in V_1
   (3) When a triphasic R wave is present in V_1, a left "rabbit ear" taller than the right (Note: A taller right "rabbit ear" does not indicate supraventricular tachycardia with aberration.)
   (4) QRS complexes pointing in the same direction, either all positive or all negative in V_1–V_6
   (5) rS (R wave smaller than S wave) or QS pattern in V_6
   b. LBBB tachycardia:
   (1) An R wave in V_1 or V_2 > 30 msec duration
   (2) A duration > 60 msec from the onset of the QRS to the nadir of the S wave in V_1 or V_2
   (3) Notching on the downstroke of the S wave in V_1 or V_2
   (4) Any Q wave in V_6

exercise test), it is likely to be SVT with aberration. During VT, the QRS complex may be very wide and oddly shaped, with a bizarre axis reflecting a ventricular focus. Typically, wide complex tachycardias are divided into left bundle branch block (LBBB) tachycardias when there is a dominant (and usually terminal) Q or S wave in V_1 (Figure 34.6) and right bundle branch block (RBBB) tachycardias when there is a dominant (and usually terminal) R wave in V_1 (Figure 34.7). Morphologic characteristics of VT have been observed in each BBB pattern (see Box 34.2).

It may not always be possible to distinguish between SVT and VT, particularly if information is limited to that from an isolated rhythm strip. When the diagnosis is unclear, it is always safer to assume a diagnosis of VT, especially in the presence of underlying heart disease. Eighty percent of all wide complex tachycardias are VT, but in patients with underlying heart disease a wide complex tachycardia is VT 95% of the time. Intravenously administered verapamil, an effective treatment for SVT, can precipitate severe hypotension and loss of consciousness in patients with VT. Adenosine, with its very short half-life, is unlikely to cause the hemodynamic collapse found with verapamil. Therefore, when a supraventricular mechanism is suspected, adenosine can be administered with relative safety. Termination of the tachycardia with adenosine does not definitively rule out VT. Adenosine should not be used, however, in the presence of active bronchospasm or myocardial

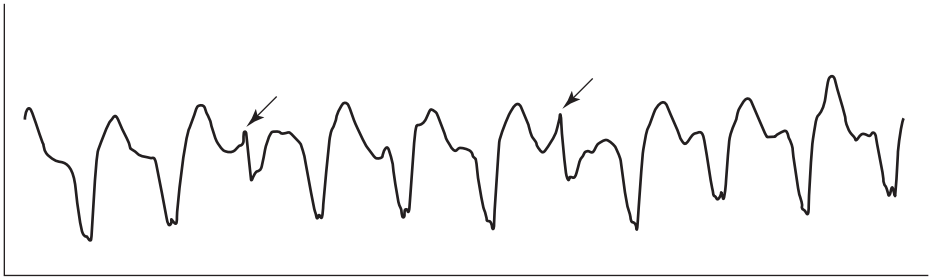


Figure 34.5 Rhythm strip during ventricular tachycardia. The intermittent narrower beats *(arrows)* represent fusion beats of ventricular tachycardia and sinus capture beats.

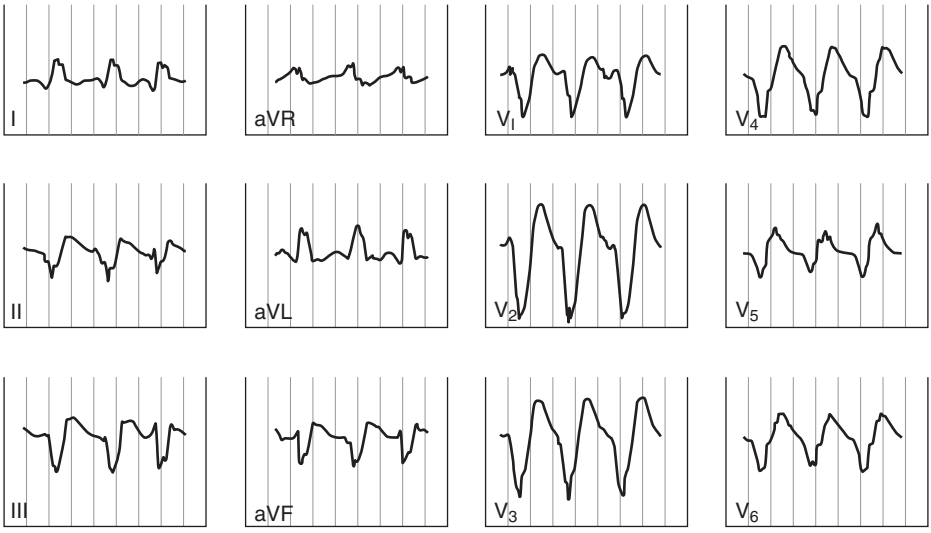


Figure 34.6 Ventricular tachycardia of a left bundle branch morphology. Leads V_1 and V_2 reveal the characteristic slurred and slow downstroke, and V_6 has a clear Q wave.

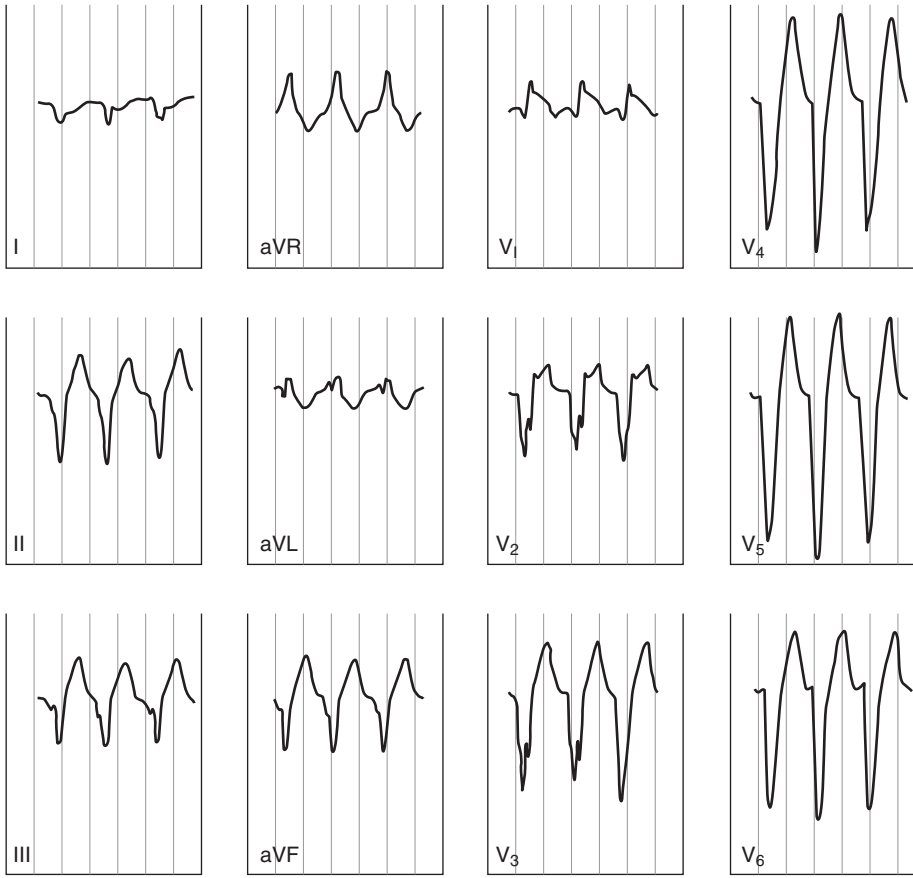


Figure 34.7 Ventricular tachycardia of a right bundle branch morphology with a typical right superior axis and wide QRS complex. The QR pattern in V_1 is a characteristic morphology and suggests a prior anteroseptal myocardial infarction.

ischemia. Intravenously administered procainamide, which can terminate many episodes of VT and SVT, is a general first-line therapy when the diagnosis is unclear.

MONOMORPHIC VENTRICULAR TACHYCARDIA

The majority of sustained monomorphic VTs occur in the setting of coronary artery disease (CAD), previous myocardial infarction, and left ventricular dysfunction. Many of these patients have a history of myocardial infarction complicated by CHF, BBB, or hypotension, which reflects extensive myocardial damage. Any patient who presents with VT, therefore, should receive an evaluation for ventricular function and CAD. Sustained VT also occurs in patients with other types of structural heart disease, such as dilated cardiomyopathies, cardiac sarcoidosis, or repaired congenital heart abnormalities. Although their long-term treatment may differ, acute therapy is essentially the same.

Acute management of VT is dictated by hemodynamic status as outlined earlier. Intravenous administration of lidocaine and procainamide is standard therapy for tolerated VT, with procainamide probably being more efficacious (Table 34.5). Procainamide, which has vasodilating

TABLE 34.5 ■ **Acute Drug Therapy for Ventricular Tachycardia**

Drug	Dosage*	Adverse Effects
Lidocaine	*For cardiac arrest:* initial bolus: 1–1.5 mg/kg *If persists:* additional bolus (0.5 mg/kg) every 10 minutes as needed; maximum dose: 3 mg/kg; infusion: 1–4 mg/min	Reduced clearance in congestive heart failure and acute myocardial infarction (decrease dose) Reduced volume of distribution in patients older than 70 years (decrease dose) Central nervous system effects include agitation, lethargy, and seizure Large doses can induce heart block
Procainamide	Loading: 17 mg/kg over 1 hour Infusion: 1–4 mg/min	Hold infusion if QRS complex widens > 50% Vasodilatation and hypotension Negative inotropic effects
Amiodarone	Oral: 800–1600 mg/day for 2 weeks, then 200–400 mg/day Intravenous: 1050–1200 mg over 24 hours	Vasodilatation Negative inotropic effects with intravenous preparations Bradycardia and heart block
Epinephrine	*For cardiac arrest:* bolus: 1 mg every 5 minutes Give through endotracheal tube if no intravenous access is available	Profound inotropic effects can precipitate ischemia Can exacerbate digoxin-toxic ventricular arrhythmias

*See Appendix D, ACLS algorithms, for more dosing guidelines.

properties, can lead to acute hypotension, making close monitoring and adequate IV access essential. Fortunately, the hypotension usually responds to slowing or discontinuing the infusion or giving IV fluids. Other adverse effects include negative inotropic effects, which can lead to decompensation in individuals with poor ventricular function and heart block in patients with underlying His-Purkinje disease. Amiodarone, available in both oral and IV forms, can also be used for refractory VT. Like procainamide, amiodarone has vasodilating effects and IV preparations can have negative inotropic effects (see Table 34.5). Acute treatment options for VT include overdrive pacing through a temporary pacing wire, an epicardial wire, or a preexisting ICD. Because attempts at overdrive pacing can result in tachycardia acceleration or VF, a defibrillator should always be readily available. Long-term therapy for monomorphic VT in patients with underlying heart disease includes antiarrhythmic drugs, an ICD, and radiofrequency catheter ablation.

A foreign body within the ventricle can also cause VT, although it is typically nonsustained. For example, brief runs of VT during placement of a guide wire, Swan-Ganz catheter, or temporary pacing wire within the right ventricle are common. The etiology is usually clear because the VT is temporally related to catheter placement and terminates with its removal or repositioning.

Polymorphic Ventricular Tachycardia

Although often lumped together, patients with polymorphic VT represent a spectrum of underlying pathologic processes. When approaching the patient with polymorphic VT, one should begin with examination and careful measurement of the QT interval of the 12-lead ECG and rhythm strip in sinus rhythm.

Polymorphic VT with Normal QT Duration

If the QT duration is normal, then myocardial ischemia is the most likely precipitating factor. In the scenario of active ischemia, IV infusion of lidocaine often has a stabilizing effect. Refractory

VENTRICULAR TACHYCARDIA IN THE ABSENCE OF STRUCTURAL HEART DISEASE

It is well known that ventricular ectopy can occur in normal hearts. Although the exact incidence is not clear, sustained VT in the normal heart is probably underrecognized. Referred to as idiopathic VT, there are two main variants of these monomorphic VTs: outflow tract VT (also referred to as adenosine-sensitive or catecholamine-sensitive VT), and idiopathic left ventricular tachycardia (also referred to as fascicular VT, Belhassen VT, or verapamil-sensitive VT).

Outflow tract VT is classically described as arising from the right ventricular outflow tract (RVOT) and has an LBBB morphology with tall R waves in the inferior leads (Figure 34.E1). These VTs arise as a result of abnormal triggered activity most commonly from sites on the RVOT septum just below the pulmonic valve, but they can also arise from the RVOT free wall or even the left ventricular outflow tract and coronary cusp region of the aortic valve (which can result in an RBBB pattern). The triggered activity of outflow tract VT is precipitated by exercise and catecholamines. The prognosis of outflow tract VT is almost uniformly good: it can be terminated by adenosine, verapamil, beta-blockers, and even vagal maneuvers. It is also highly amenable to catheter-based ablation procedures.

Idiopathic left ventricular tachycardia (ILVT) arises from the mid inferoseptal left ventricle in the region of the left posterior fascicle, generally the result of a reentrant mechanism. Involvement of the conduction system results in a relatively narrow QRS with an RBBB morphology and left axis deviation (Figure 34.E2); ILVT is often confused for SVT because of this QRS morphology. Like outflow tract VT, it can be initiated with exercise (although less frequently) and generally has a good prognosis. It can be terminated and prevented with verapamil and is also amenable to catheter-based ablation.

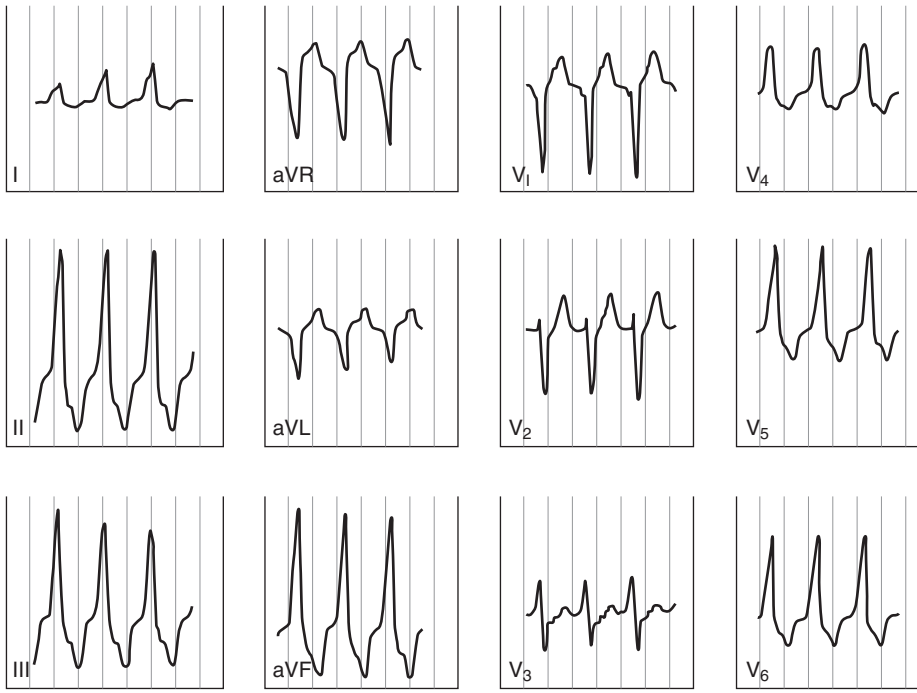


Figure 34.E1 Idiopathic ventricular tachycardia originating from the right ventricular outflow tract. Note the typical left bundle branch morphology and inferior QRS axis (i.e., positive [upright] QRS complexes in leads II, III, and aVF).

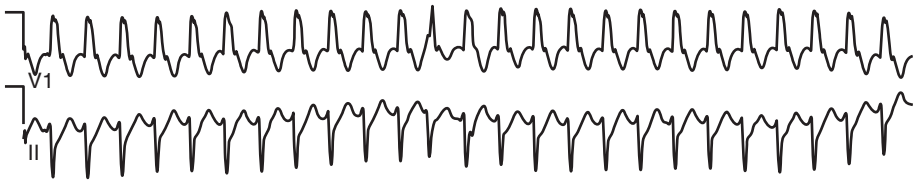


Figure 34.E2 Idiopathic left ventricular tachycardia (ILVT) arising from the left posterior fascicular region, with a right bundle branch block pattern and left axis deviation.

polymorphic VT and VF may respond to IV infusion of amiodarone. Treatment of active ischemia with beta-blockers, nitrates, antiplatelet therapy, and anticoagulation is important to the treatment of the electrical instability. Patients with suspected ischemia should receive a prompt cardiac catheterization and revascularization when appropriate. Revascularization alone may not provide adequate protection against recurrence of polymorphic VT, however, and an ICD may be required for long-term management, especially in patients with reduced left ventricular function.

Polymorphic VT with Prolonged QT Duration

If the QT duration is prolonged in the setting of polymorphic VT, then it falls into a separate category, referred to as "torsades de pointes" (or "torsades" for short). Classically, the QRS complexes exhibit a phasic "twisting" around the isoelectric line. Phasic variation in QRS amplitude and polarity should be observed in two or more leads because variation in a single rhythm strip may be misleading. The QT prolongation may be idiopathic (referred to as congenital long QT) or acquired in the setting of medications and electrolyte derangements. Typically, there is baseline sinus bradycardia, which adds to the absolute QT interval prolongation and predisposes to the generation of premature beats (Figure 34.8). Torsades has even been noted in patients with a normal baseline QT who have a prolonged pause (i.e., from sinus node arrest or complete heart block), followed by a beat with a significantly prolonged QT coupled with a premature ventricular beat.

In the ICU, acquired long QT occurs frequently. Many drugs used in the ICU, especially haloperidol, can precipitate QT abnormalities and torsades (Box 34.3). The University of Arizona maintains a comprehensive list of drugs that can cause QT prolongation at http://QTdrugs.org. Other underlying conditions that may set the stage for torsades include electrolyte imbalance (particularly hypokalemia and hypomagnesemia), hypothyroidism, intracranial events, myocardial

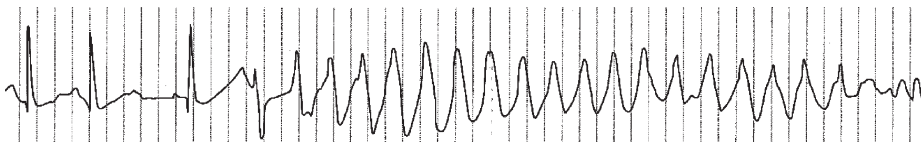


Figure 34.8 The top tracing initially shows sinus rhythm with a long QT interval followed by onset of torsades de pointes after an atrial premature contraction.

BOX 34.3 ■ Drugs Associated with Torsades de Pointes

Class IA antiarrhythmic agents (quinidine, procainamide, disopyramide)
Class III antiarrhythmic agents (sotalol, d-sotalol, amiodarone, bretylium, dofetilide, sematilide)
Other agents with antiarrhythmic properties (bepridil, encainide, propafenone, ajmaline, aprindine)
Psychotherapeutic drugs
Haloperidol
Phenothiazines (chlorpromazine, thioridazine)
Serotonin reuptake antagonists (citalopram, fluoxetine, paroxetine, quetiapine)
Tricyclic and tetracyclic antidepressants
Antihistamines (terfenadine, astemizole)
Antimicrobials (azithromycin, erythromycin, moxifloxacin, trimethoprim-sulfamethoxazole, pentamidine)
Poisons (organophosphate insecticides, arsenic)
Miscellaneous (selected antimicrobials,* chloral hydrate, lidoflazine, methadone, prenylamine, probucol, terodiline)

**Macrolide antibiotics, antifungals (such as fluconazole or ketoconazole), and HIV (human immunodeficiency virus) protease inhibitors (such as indinavir or ritonavir).*

ischemia, starvation, and anorexia nervosa. Some investigators suggest that patients with congenital long QT are susceptible to the acquired forms of torsades de pointes. Torsades de pointes may occur in self-terminating salvos, which may be asymptomatic or result in syncope. It is critical to consider drug-induced torsades in any patient with runs of polymorphic VT and a prolonged QT interval. When such episodes are correctly identified, appropriate treatment may prevent a cardiac arrest. Initial therapy involves discontinuation of precipitating agents and correction of electrolyte and metabolic abnormalities. When an arrest has occurred, direct cardioversion is at least transiently effective. An IV bolus of magnesium may have stabilizing effects during resuscitation or long runs of polymorphic VT. Because acquired torsades is predominantly bradycardia or pause dependent, interventions also aim to increase heart rate. Isoproterenol infusion at doses of 2 to 10 mcg/min is a readily available method of increasing sinus rate but can be potentially hazardous in patients with CAD and left ventricular dysfunction as it has vasodilatory effects and can cause acute hypotension. Temporary pacing (both atrial and ventricular) is an effective method, but its use is dependent on the availability of trained personnel. Atropine can be used as third-line management when other treatment modalities are unavailable.

In contrast, first-line therapy for patients with congenital long QT is with beta-blockers, titrated to the maximum tolerated dosage. Beta-blockers also blunt the sympathetic response, which can trigger an episode of torsades. It is critical to avoid any medications that can further prolong the QT interval and precipitate episodes of tachycardia. Some patients, particularly resuscitated sudden death survivors, require ICDs.

Special Considerations

VENTRICULAR FIBRILLATION

Ventricular fibrillation in the ICU setting may occur either in patients with underlying heart disease, particularly ischemic heart disease, or as the end result of profound hypoxemia, acidosis, electrolyte derangements, and hypotension from noncardiac causes. In these latter situations, ultimate recovery depends on adequate oxygenation, tissue perfusion, and resolution of underlying disease. Successful resuscitation depends on prompt defibrillation, and several high-energy defibrillation attempts may be necessary. Boluses of epinephrine and amiodarone may aid in resuscitation attempts when repeated defibrillation attempts are initially unsuccessful (see Appendix D for ACLS algorithms).

DIGOXIN TOXICITY

Digoxin is a commonly prescribed drug in patients with left ventricular dysfunction and atrial arrhythmias, but toxic levels can be life threatening. Unfortunately, the first signs and symptoms of digoxin toxicity are easily overlooked. The extracardiac manifestations are relatively nonspecific: fatigue, anorexia, nausea, headache, confusion, and visual symptoms. Factors associated with increased risk for toxicity include renal insufficiency, electrolyte derangements (especially hypokalemia and hypomagnesemia), advanced pulmonary disease, and concomitant treatment with agents that increase serum digoxin levels such as quinidine or amiodarone. Patients receiving digoxin in the ICU are clearly at increased risk for toxic side effects.

Digoxin affects all types of cardiac tissue. Typically, in sinus rhythm, digoxin at therapeutic levels can slow the heart rate through decreased adrenergic tone without significant effects on atrial tissue. At toxic levels, however, it can increase the automaticity of atrial tissue, resulting in atrial tachycardia with upright P waves in the inferior limb leads and V_1. Toxic levels may also result in increased automaticity of AV junctional tissue, resulting in a junctional tachycardia (see Table 34.1). When there is underlying atrial fibrillation, this junctional tachycardia results in a paradoxical regularization of RR intervals. AV conduction is slowed by digoxin, however, and

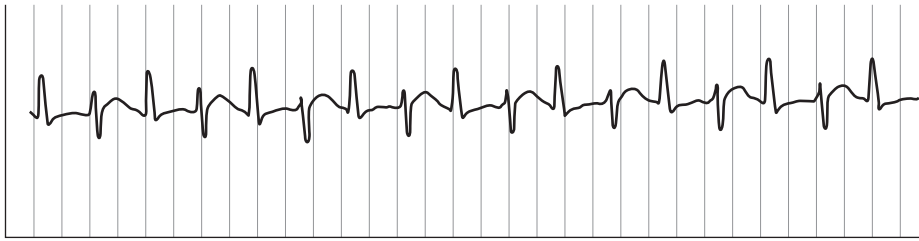


Figure 34.9 Bidirectional ventricular tachycardia in the setting of digoxin toxicity. The alternating morphologies reflect the alternating foci of the left posterior fascicle and the left anterior fascicle.

may result in advanced AV block at toxic levels (see Chapter 33). Digoxin toxicity should be suspected whenever the combination of increased automaticity and depressed AV conduction is observed. Digoxin also affects ventricular tissue, primarily through enhanced automaticity and triggered activity. The most common manifestation is frequent ventricular premature beats. Sustained bidirectional VT and fascicular tachycardia (Figure 34.9) are highly sensitive markers of digoxin toxicity.

Effective treatment of digoxin toxicity depends on prompt recognition. When the manifestations do not result in hemodynamic consequences, drug withdrawal and electrolyte correction suffice. VT, however, demands more aggressive management. F(ab) fragments of digoxin-specific antibodies are the treatment of choice for life-threatening digoxin toxic rhythms. Most patients show some response within 20 minutes after their infusion. Their most prominent adverse effect is the rapid development of hypokalemia, presumably resulting from sodium pump reactivation. When F(ab) fragments are unavailable or an immediate response is required for VT, the most useful drugs are lidocaine and phenytoin, both of which have little effect on AV conduction. If DC cardioversion of sustained VT is required, one should be prepared for emergency pacing, as there may be concomitant underlying AV block. Beta-blockers can further depress AV conduction but may prove effective in reducing automaticity. Overdrive pacing can result in tachycardia acceleration and should not be attempted.

TACHYCARDIAS THAT DO NOT REQUIRE IMMEDIATE INTERVENTION

Not all tachycardias require immediate intervention. It is not unusual to observe self-limited paroxysms of tachycardia that are not hemodynamically significant in the ICU. Patients with pulmonary or cardiac disease, for example, may have paroxysms of *atrial tachycardia* that are entirely asymptomatic. Suppression of such self-limited episodes with antiarrhythmic agents may cause significant side effects and is not indicated. *Nonsustained VT* is also common in patients with cardiac disease. Although nonsustained VT is a marker of risk for sudden death and may require further evaluation, suppression of self-limited ventricular ectopy is not indicated. In fact, suppression of ventricular ectopy with antiarrhythmic medications may be associated with increased mortality.

POSTOPERATIVE CARDIAC PATIENTS

Patients experience a variety of atrial and ventricular tachyarrhythmias after open-heart surgery, typically within the first 72 postoperative hours. Inflammation of the pericardium and trauma to the atria during surgery, plus digitalis toxicity, may precipitate atrial fibrillation, flutter, and atrial tachycardias. AV junctional tachycardia occurs frequently secondary to trauma during surgery. When the type of SVT is not clear, recordings from the temporary epicardial wires can help

identify atrial activity and clarify the AV relationship. Atrial wires also permit overdrive pacing of atrial flutter, atrial tachycardia, and junctional tachycardias.

Because most arrhythmias in the immediate postoperative period are exacerbated by high sympathetic tone, a beta-blocker is the logical first-line agent in patients without contraindications. Prophylactic use of beta-blockers has been shown to decrease the incidence of postoperative SVT. Although it is still frequently used, digoxin poorly controls ventricular response to atrial arrhythmias. Circulating catecholamines overwhelm its vagomimetic effects, and the large doses that are necessary to achieve adequate control often result in toxic levels.

Nonsustained VT also occurs postoperatively in up to 50% of cardiac surgery patients. Typically, it occurs within the first 12 to 24 hours and is limited to short runs. Electrolyte disturbances, perioperative myocardial ischemia, and beta-blocker withdrawal can increase the frequency of the VT. Correction of precipitating causes is the mainstay of therapy for nonsustained VT. In contrast, sustained VT or long runs of nonsustained VT that are hemodynamically significant require further evaluation and management. Standard cardioversion and antiarrhythmic therapy as discussed earlier can be used acutely. Temporary ventricular pacing wires may be used to overdrive pace VT, but there is always a risk of accelerating the tachycardia and precipitating VF.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

The majority of patients with an ICD have underlying heart disease as well as a host of comorbid conditions, any of which may result in an ICU admission. There are some important basic facts to remember when caring for these patients in an acute setting. First, the presence of an ICD does not preclude external defibrillation. If a patient has a hemodynamically unstable tachycardia and the ICD is not effectively terminating it, one should not hesitate to perform standard external defibrillation. Likewise, if a patient requires it, one should not hesitate to perform cardiopulmonary resuscitation. Touching the patient while the device is charging or delivering a shock results only in a buzzlike sensation. One will *not* be shocked.

Inappropriate, and possibly incessant, device discharges for sinus tachycardia, SVT, or even well-tolerated VT may also be encountered. Many current ICDs are programmed to discriminate between SVT and VT, but these discriminators are not perfect and may still deliver inappropriate therapies. In the event that the ICD is delivering inappropriate shocks, placing a magnet over the generator will temporarily disable it from shocking the patient; the device returns to baseline settings once the magnet is removed. Securing a magnet over the ICD may also be used in the operating suite if a patient requires emergency surgery—the device must be inactivated before electrocautery (and electromyographic studies) to avoid spurious discharges. Finally, patients with an ICD should not undergo magnetic resonance studies except in centers with experienced radiologists and electrophysiologists collaborating who can on occasion perform such studies safely.

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CHAPTER 35

Barotrauma and Chest Tubes

Travis M. Polk ■ Patrick M. Reilly

Barotrauma refers to lung injury caused by high ventilatory pressures. Despite heightened awareness of ventilator-induced lung injury (VILI) resulting from alveolar hyperinflation, barotrauma remains a common complication of mechanical ventilation. For example, the incidence of pneumothorax with positive pressure ventilation in intensive care unit (ICU) patients is 4% to 15%.

Rupture of alveoli typically occurs when peak airway pressures exceed 40 to 50 cm H_2O. As peak airway pressures approach 70 cm H_2O, the incidence may exceed 40%. When the interstitial-alveolar pressure gradient is exceeded, alveolar rupture results in air tracking along the peribronchial vascular sheath into the interstitium. This air can then propagate further, dissecting along any of the contiguous planes of the body and resulting in a variety of complications, from fairly benign to rapidly lethal (Box 35.1).

Manifestations of Barotrauma

Subcutaneous emphysema is typically a benign finding but, when present, an inadequately decompressed or undiagnosed pneumothorax must be considered. However, in the absence of a pneumothorax, prophylactic chest tubes are usually not recommended unless the subcutaneous air is compromising respiration or hemodynamics. In severe cases, subcutaneous bullae can result in tension physiology necessitating decompression with infraclavicular "blowholes" (e.g., cutaneous slits, or *gills*) or placement of subcutaneous catheters.

Nearly all *simple pneumothoraces* associated with mechanical ventilation should be managed with tube thoracostomy. Traditionally, this has been accomplished with large bore chest tubes. However, smaller caliber chest tubes and pigtail-type catheters are likely equally efficacious. The exception to this thoracostomy mandate is the finding of *traumatic occult pneumothorax*, which is visible only on cross-sectional imaging (e.g., computed tomography [CT]) and which, when present, may be closely observed if the patient is otherwise clinically stable. The diagnosis of pneumothorax with portable chest radiographs (chest radiographs may be difficult in the ICU, particularly in the supine patient. A chest CT scan may be necessary to make this diagnosis, particularly with anterior pneumothoraces. For patients who are felt to be too unstable to travel to the radiology suite, ultrasound can be a useful diagnostic adjunct. The intensivist can readily learn techniques for visualizing pneumothorax with ultrasound at the bedside, and these methods have high reported positive predictive values.

Tension pneumothorax remains one of the most feared complications in the ICU. If left untreated, it can rapidly lead to hemodynamic and respiratory instability and potentially cardiorespiratory arrest. Classic signs and symptoms include absent breath sounds, jugular venous distention, and tracheal deviation; however, these are frequently unreliable and difficult to assess in the mechanically ventilated patient. Unexplained tachycardia and hypotension,

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increasing central venous pressures, as well as increasing peak airway and plateau pressures and diminishing tidal volumes are more reliable signals of a developing tension pneumothorax in the critically ill patient. Tube thoracostomy should be performed expeditiously if a tension pneumothorax is suspected. If the patient is in extremis or in cardiac arrest, immediate decompressive needle thoracostomy may be attempted. This involves placement of a long 14-gauge angiocatheter in the second intercostal space at the midclavicular line. However, it is important to recognize that clinical, cadaveric, and radiologic studies have demonstrated significant shortfalls with this technique. If needle thoracostomy at the second intercostal space fails to result in clinical improvement, then an immediate tube or needle thoracostomy should be performed in the midaxillary line at the fifth intercostal space. If needle thoracostomy is performed, this should be followed by proper tube thoracostomy as soon as the clinical situation allows.

Pneumomediastinum is usually a manifestation of the same pathophysiology as pneumothorax. However, causes such as tracheoesophageal injury or mediastinitis resulting from descending neck infection should be excluded. In the absence of such findings, observation for the development of pneumothorax or respiratory compromise is usually sufficient.

Pneumopericardium is uncommon and may be related to trauma, extension from a pneumomediastinum, or occasionally pyogenic lung abscess. In the most severe cases, tension pneumopericardium may develop and result in cardiac tamponade necessitating immediate aspiration or surgical decompression.

Pneumoperitoneum occurs uncommonly when air may track from ruptured alveoli into the retroperitoneum or peritoneal cavity. This may be difficult to discriminate from free air caused by injury to a hollow viscus. When present, abdominal CT, diagnostic peritoneal lavage, or even exploratory surgery may be necessary to elucidate the cause.

Systemic gas embolization may occur when air tracks along the peribronchial vascular sheath and encounters either a vascular disruption or a severe parenchymal infiltrate that blocks further dissection of the air. Adverse effects of this phenomenon may include circulatory collapse, cerebral infarction, seizures, or myocardial injury. Treatment considerations should include aggressive cardiopulmonary resuscitation, hyperoxygenation, and maintenance of adequate vascular volume. In the case of neurologic symptoms caused by arterial air embolism, consideration should be given to systemic anticoagulation and hyperbaric oxygen treatment (Chapter 56). For large venous air embolisms, partial aspiration via a right atrial catheter may be attempted.

BOX 35.1 ■ Spectrum of Clinical Manifestations of Extra-alveolar Gas

Benign end of spectrum
Pulmonary interstitial emphysema
Subpleural air cysts
Subcutaneous emphysema
Pneumomediastinum
Pneumopericardium
Pneumoperitoneum
Pneumoretroperitoneum
Pneumothorax
Tension pneumothorax
Systemic gas embolization
Life-threatening end of spectrum

Chest Tube Selection, Insertion, and Management

INDICATIONS AND SELECTION OF TUBES

Pneumothorax is the most common indication for chest tube placement in the ICU. However, other indications may include effusion, hemothorax, or empyema (Box 35.2). In the emergent setting, a large bore tube is always preferable, particularly if the exact cause of the patient's deterioration is unclear. However, in an elective setting, the current trend is to place smaller caliber tubes whenever possible in order to minimize patient discomfort and to promote effective pulmonary toilet.

INSERTION TECHNIQUE: TRADITIONAL CHEST TUBES (20-40 Fr)

Chest tube insertion (tube thoracostomy) is not without risk and requires sufficient expertise in the procedural aspects as well as the management of potential complications associated with the procedure (Box 35.3). The procedure is most easily performed with the patient in the supine position and the ipsilateral arm abducted or resting over the patient's head. Patients who are hemodynamically stable may receive preprocedural sedation. In awake patients, analgesia should always

BOX 35.2 ■ Indications for Tube Thoracostomy in the Intensive Care Unit

- Pneumothorax
  - —Barotrauma
  - —Iatrogenic
  - —Spontaneous
- Traumatic
  - —Hemothorax
  - —Iatrogenic
  - —Traumatic
- Hydrothorax
  - —Malignant
  - —Sympathetic
- Bronchopleural fistula
- Chylothorax
- Empyema
- Penetrating chest injury
- Postoperative thoracotomy
- After needle decompression
- Prophylactic (in patients with rib fractures prior to starting positive-pressure ventilation)

BOX 35.3 ■ Complications of Tube Thoracostomy

- Hemorrhage (resulting from the laceration of intercostal artery, muscle, or vein)
- Lacerated lung
- Bronchopleural fistula
- Cardiac injury
- Subcutaneous tube placement
- Intraperitoneal placement (with or without hepatic or splenic injury)
- Infection (cellulitis, empyema)
- Allergic reactions (from local anesthetics, skin preparation, or tape)
- Damage to intercostal nerve

be administered. Although intercostal nerve blocks are possible, the easiest method to administer analgesia is by direct injection of local anesthetic solution around the region of planned entry. The key anatomic landmark is the fifth intercostal space at the midaxillary line, which corresponds to the nipple or inframammary fold. Once the chest wall is prepped and draped in the usual sterile fashion, local anesthetic is infiltrated into the area. An incision large enough to accommodate the tube and one finger is made in the skin and carried down through the subcutaneous tissue. An extrathoracic tract is then developed using a large Peon or Kelly clamp down to the sixth rib. Additional local anesthetic is injected into the intercostal muscles and pleural space. The clamp is then used to gently spread the intercostal muscles above the sixth rib and then pass over the rib into the pleural space. Following a large spread of the clamp, a finger is inserted into the pleural space and a careful exploration should be performed to confirm intrathoracic position and free any pleural adhesions. Using the finger still in the chest, a chest tube is inserted with a clamp and guided in the cranioposterior direction. The tube is advanced gently until slight resistance is met and then secured in place with heavy suture. Of note, the numbers on the side of most chest tubes represent the distance in centimeters from the last "sentinel" hole, *not* from the end of the chest tube itself. A chest radiograph should be obtained for confirmation of position and to identify the location of the sentinel hole of the chest tube (signified by a break in the radio-opaque line on the chest tube). Malpositioned chest tubes require replacement and should never be advanced further into the chest following placement because of the risk of infection.

Chest tube placement using sharp trocars has been associated with intra-abdominal, intrathoracic and cardiac injuries and is not recommended.

INSERTION TECHNIQUE: SMALL BORE TUBE/PIGTAIL CATHETER

The use of smaller chest tubes and pigtail catheters for the management of pneumothoraces, pleural effusions, and even hemothoraces is becoming increasingly common. There are many variations of these catheters but, regardless of type, most are placed via a modified Seldinger technique (see Figure 11.1, Chapter 11). The pleural space can be accessed with a needle and syringe. Upon entry into the pleural space, a wire can be passed through the needle and the needle subsequently removed. A dilator is passed over the wire to create a tract, after which a catheter is advanced over the wire. Again, a chest radiograph upon completion of the procedure is highly recommended to confirm adequate placement and resolution of the intrapleural pathology.

PROPHYLACTIC ANTIBIOTICS

Infections related to chest tube insertion are rare and usually a result of *Staphylococcus aureus* or *Streptococcus* species. Although there are some data to suggest that a single dose of preprocedural antibiotics is associated with decreased infectious complications, including both pneumonia and empyema, there remains no strong evidence to support this practice for either spontaneous pneumothorax or effusion (benign or malignant). There is, however, strong evidence to support the administration of antibiotics prior to tube thoracostomy in trauma patients who have sustained penetrating or blunt chest trauma. In these cases, a single dose of a first-generation cephalosporin or clindamycin prior to the procedure is appropriate. The benefit of a longer course of antibiotics for prophylaxis is of unproven value and is not recommended.

DRAINAGE SYSTEMS

Immediately after placement, chest tubes should be connected to a drainage system. The most common system, Pleur-evac, utilizes a disposable three chamber system (Figure 35.1). With this system, the chest tube effluent drains into a collection chamber that is marked for accurate

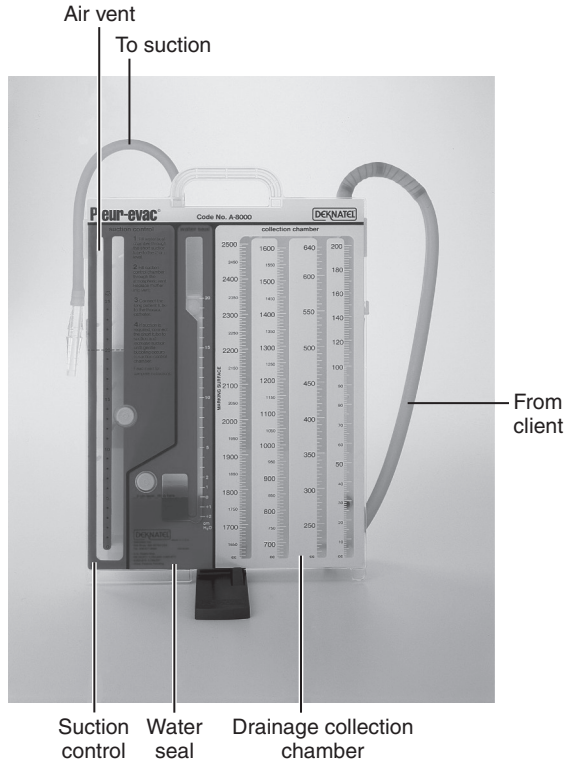


Figure 35.1 Three chamber system for chest tube drainage. *(From Potter PA, Perry AG: Fundamentals of Nursing, 7th ed, St. Louis: Mosby, 2009.)*

recording of the output. The collection chamber is connected, in series, to a water seal chamber that acts as a one-way valve allowing air to exit the pleural space. The water seal chamber is then attached, in series, to a suction chamber. The amount of water in the suction chamber determines the amount of negative pressure in the pleural space when the apparatus is attached to wall suction. This is ordinarily filled to −20 cm H_2O except in special circumstances. A new "dry" suction variant of the three-chamber drainage system has become increasingly popular because it replaces the wet suction chamber with an adjustable dial that allows titration of the amount of pressure.

Continuous air bubbling in the water seal chamber indicates an air leak. If this occurs, it is imperative to determine where the leak is originating. Leaks can occur from within the lung, within the chest tube, or within the drainage system. Air entry from within the lung may represent a laceration to the lung parenchyma or a bronchopleural fistula. Leaks from the chest tube can occur from damage to the tubing or, more commonly, inadvertent withdrawal of the tube resulting in the sentinel eye being outside of the body. A drainage system leak is usually due to a loose connection or an inadequately sealed insertion site.

Patency of a chest tube is evaluated with the tube on water seal (suction off). A patent tube demonstrates fluctuations in the water seal chamber fluid level or fluid within the tube with respirations ("tidaling"). A nonfunctional tube should be removed immediately, as it serves no purpose and carries only the risk of infection.

Rarely utilized, the Heimlich valve is a one-way flutter valve that can be attached to the end of a chest tube without requiring suction. This can be utilized for patient transport or, in cases of slowly resolving air leaks, the patient can be managed as an outpatient with this valve attached to the patient's chest tube.

MONITORING OF CHEST TUBES

Once placed, chest tubes should be monitored closely for air leaks (as described earlier), as well as the amount and character of effluent (Table 35.1). Additionally, regular chest radiographs should be followed to assure that adequate expansion of the lung is maintained. The necessity for chest drains should be reassessed on a daily basis and should be discontinued at the earliest possible opportunity to minimize patient discomfort and infectious complications. Improving lung aeration is often challenging in patients with chest tubes. Secretion clearance is paramount and incentive spirometry may be used as an objective and quantifiable tool to measure a patient's progress. Optimal pain control is necessary to encourage deep breathing and may require a multifaceted aggressive approach including nonsteroidal anti-inflammatory agents, opioids, or regional and neuraxial analgesics (Chapter 87).

CHEST TUBE MANAGEMENT AND REMOVAL

Figure 35.E1 presents an algorithm for chest tube management in patients with pneumothorax, pleural effusion, or hemothorax. After placement, chest tubes should typically be placed on −20 cm H_2O of suction for a period of at least 24 hours. After this, if the lung is fully expanded on chest radiograph and there is no air leak, suction can be removed and the chest tube should be placed on water seal. A chest radiograph should be obtained after 4 to 24 hours on water seal to ensure that the lung remains fully expanded.

In general, chest tubes should never be clamped. However, rarely, the tube can be clamped to evaluate whether there is a very slow air leak that is not apparent on water seal. This maneuver is not without risk, as no safety mechanism is available for decompression of the chest and a tension pneumothorax may develop (unlike the method described previously with the tube on water seal). Thus, this method should be only be used with the utmost caution and only if personnel are immediately available to unclamp the tube if hemodynamic instability occurs.

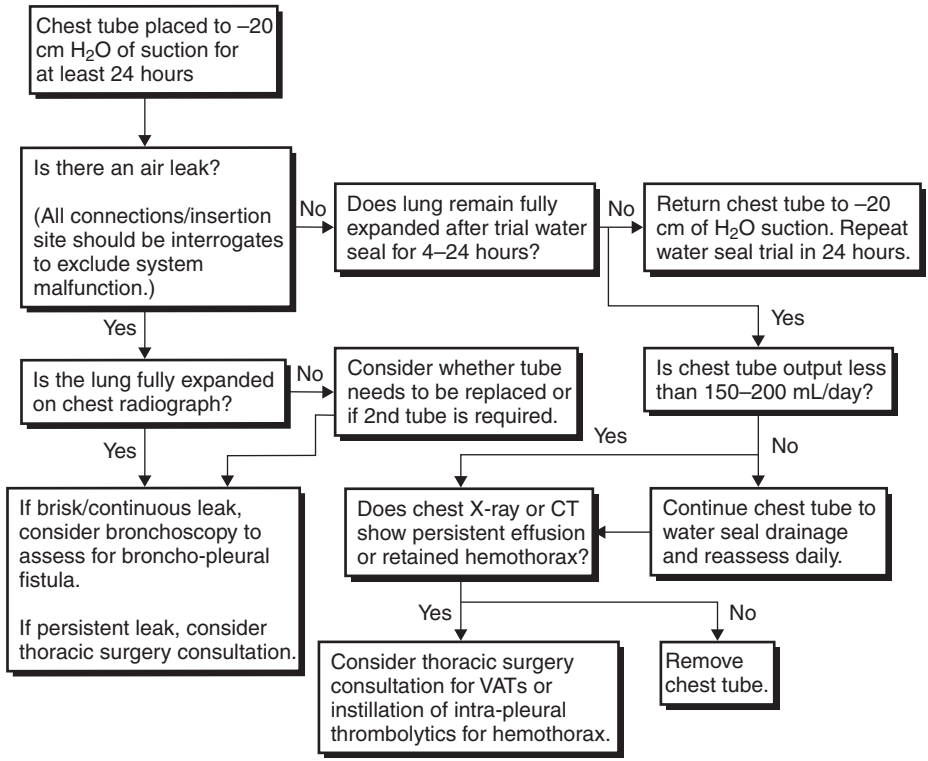


Figure 35.E1 Schematic flow diagram to guide management of chest tube for pneumothorax, pleural effusion or hemothorax in intensive care unit patients. See text for details. CT, computed tomography; VATS, video-assisted thoracoscopic surgery.

TABLE 35.1 ■ **Troubleshooting Chest Tube Problems**

Problem	Cause	Intervention
Lung not reexpanded	Subcutaneous tube	Remove tube and place new tube in proper position
	Intraperitoneal tube	Remove tube and place new tube in proper position; assess for intra-abdominal injury
	Side port of tube is subcutaneous	Remove tube and place new tube in proper position
	Plugged tube	Remove tube and place new tube in proper position
	Plugged bronchus	Bronchoscopy
	Large air leak	Check all connections; increase suction; consider Emerson pump; place second chest tube
	Entrapped lung secondary to empyema	Operative decortication
Fluid in chest not drained	Tube located too high	Place second chest tube closer to the diaphragm and posteriorly
	Clotted hemothorax	Operative debridement
	Loculated fluid	Computed tomography–guided placement of new tube or operative drainage
	Fluid too thick (empyema)	Emerson pump or operative drainage
Continuous air leak	Large parenchymal leak	Place second tube; evaluate for bronchial injury
	Side port of tube is subcutaneous	Remove tube and place new tube in proper position
	System leak	Tighten all tubing connections; replace leaking tube
	Bronchopleural fistula	Decrease ventilator pressures; operative intervention; use Emerson pump
Water seal chamber not "tidaling"	Chest tube is clotted or kinked	Replace tube
	Lung is fully reexpanded	Remove tube
	Tube is on suction	Remove suction temporarily
	High PEEP on ventilator	Decrease PEEP if possible (Note: Problem may be a nonfunctional tube instead of high PEEP.)

PEEP, positive end-expiratory pressure.

The timing of chest tube removal is often a difficult decision and depends largely on the reasons for initial chest tube placement, as well as the quantity and character of the output. Situations such as empyemas, malignant effusions, retained hemothoraces, and persistent air leaks may require that the tube remain in for an extended period of time. However, in the majority of situations, prior to chest tube removal, *all* of the following criteria should be met:

1. The quantity of fluid draining from the chest is less than 100 to 200 mL/day.
2. No air leak is noted in the water seal chamber.
3. No pneumothorax or retained hemothorax is apparent on radiographic images after the chest tube has been placed on water seal.

In general, once these three criteria have been met, the chest tube may be removed. Although controversy remains concerning the optimal technique for chest tube removal, whether the tube is removed at maximal inspiration or expiration does not appear to matter. Regardless of the method used, however, the procedure should be performed swiftly and the tube entry site must be immediately covered with an occlusive dressing of petroleum gauze, gauze, and silk tape or a

comparable alternative to avoid entrainment of air into the pleural cavity with inspiration. Alternatively, some clinicians favor the use of a purse-string suture (usually placed loosely after tube insertion and left in place) that is tied as the chest tube is removed. This technique may be most useful in thin patients with very little subcutaneous tissue to seal the chest tube tract.

Chest tubes that are placed for an empyema require different management. Empyemas obliterate the pleural space and must be managed similar to an abscess cavity. Once any air leak is resolved, these "empyema" tubes can be trimmed at the level of the skin and simply left to gravity drainage because it is virtually impossible to collapse these lungs. The chest tubes are then slowly eased out of the chest as the abscess cavity is allowed to drain and heal by secondary intention. When necessary, additional pigtail catheters can be placed by interventional radiology into noncontiguous loculated collections.

Likewise, tubes placed for malignant effusions, persistent air leaks, or retained hemothorax will frequently require specialized management. For persistently draining effusions, long-term indwelling pleural catheters can be placed, or alternatively, the patient may undergo pleurodesis via the chest tube with a variety of agents including talc, antibiotics, and anti-neoplastics. Patients with persistent air leaks following pneumothorax should have surgical consultation for potential mechanical pleurodesis or other intervention depending on the etiology of the air leak. Finally, retained hemothorax has been associated not only with increased acute infectious complications, such as empyema, but also with the development of a debilitating fibrothorax. Therefore, current recommendations advocate early consideration of video-assisted thoracoscopic surgical (VATS) drainage (or intrapleural instillation of thrombolytics in poor surgical candidates) if the chest radiograph has not cleared within a few days.

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CHAPTER 36

Change in Mental Status

Michael G. Shashaty ■ Paul N. Lanken

The patient who has a change in mental status upon admission to the intensive care unit (ICU) or while in the ICU presents a common diagnostic and management challenge. Newly admitted patients often have an unknown baseline, whereas hospitalized patients may have inconsistently or ambiguously documented mental status. Furthermore, these patients are generally unable to provide a reliable history. Most important, alterations in mental status may indicate new, potentially life-threatening pathologic processes. With many potential etiologies, an efficient yet thorough evaluation is critical. This chapter describes a systematic approach to the ICU patient with a change in mental status.

Definition

Altered mental status (also referred to as "a change in mental status [MS]" or "delta MS") is a vague but commonly used term that is applied to both alterations in level of consciousness and alterations in cognitive function (cognition, attention, awareness). Level of consciousness can be quickly characterized according to the AVPU scale (Box 36.1). This simplification of the Glasgow Coma Scale is easy to remember and document. Additionally, the ordered continuum allows for tracking of changes in level of consciousness, whereas nonspecific terms such as *stuporous* or *lethargic* do not conform to a clear hierarchy. After establishing level of consciousness, cognitive function is assessed to further detail the nature of the disturbance. A commonly used alternative scale to follow level of sedation and agitation in ICU patients is the Richmond Agitation-Sedation Scale or RASS (which is described in more detail in Chapters 5 and 37).

Changes in mental status can arise by two mechanisms: (1) disruption of function in the brain stem reticular activating system or, more commonly, (2) through processes affecting both cerebral hemispheres. Severe dysfunction produces *coma,* defined as an unresponsive and unarousable state. Less severe dysfunction produces an acute confusional state in which the patient may be sleepy, disoriented, or inattentive but responds to some stimuli in a purposeful manner. The term *delirium* is more specific than just being confused or disoriented. *Delirium* is defined as an acute change or fluctuation in mental status combined with inattention and either an altered level of consciousness or disorganized thinking. Delirium is common in ICU patients, with an incidence of 50% or higher (see Chapter 37 for details about diagnosis and management of delirium).

An acute change in mental status is distinct from dementia, aphasia, or psychiatric decompensation. An acute confusional state lasts for hours to days; in contrast, *dementia* has a much longer time course and is associated with fewer fluctuations in attention and perception. *Aphasia* can be detected by careful examination of language function. *Psychiatric conditions* that can mimic an acute confusional state include schizophrenia, depression, mania, autism, and dissociative states. *Seizures* can also produce a confusional state during the period of actual epileptic discharge or for minutes to hours during the immediate postictal period. Because details of a

Additional online-only material indicated by icon.

BOX 36.1 ■ AVPU Scale: A Simplification of the Glasgow Coma Scale

A = Alert
V = Responsive to Voice
P = Responsive to Pain
U = Unresponsive

TABLE 36.1 ■ **Signs and Symptoms Helpful in Determining Change in Mental Status**

Sign/Symptom	Association
Asterixis	Metabolic encephalopathy
Ataxia	Ethanol or sedative intoxication, Wernicke encephalopathy
Bradycardia	Hypothyroidism, cholinergic drug, digoxin toxicity
Constricted pupils	Opioid intoxication, pontine stroke
Dilated pupils	Head trauma, anticholinergic or sympathomimetic drug intoxication, ethanol or sedative withdrawal, postictal state, brain death, status/post iatrogenic pupillary dilatation
Fever	Infection, anticholinergic drug intoxication, ethanol withdrawal, neuroleptic malignant and serotonin syndromes, malignant hyperthermia
Headache or meningismus	Meningitis, subarachnoid hemorrhage
Hypertension	Hypertensive encephalopathy, anticholinergic or sympathomimetic drug intoxication, ethanol or sedative withdrawal
Hyperventilation	Central neurogenic hyperventilation, hepatic encephalopathy, hyperglycemia with diabetic ketoacidosis, sepsis, metabolic acidosis
Hypothermia	Sedative intoxication, hepatic encephalopathy, hypoglycemia, hypothyroidism, sepsis, uremia, adrenal insufficiency
Hypoventilation	Sedative or opioid intoxication
Nystagmus or ophthalmoplegia	Ethanol or sedative intoxication, Wernicke encephalopathy, vertebrobasilar ischemia, phenytoin
Papilledema	Hypertensive encephalopathy, intracranial mass, acute hydrocephalus
Rigidity	Neuroleptic malignant and serotonin syndromes, opioid reaction, dystonic reaction, hypocalcemia
Seizures	Ethanol or sedative withdrawal, theophylline toxicity, hypoglycemia, severe alkalosis
Tachycardia	Anticholinergic or sympathomimetic drug intoxication, ethanol or sedative withdrawal
Tremor	Sympathomimetic drug intoxication, ethanol or sedative withdrawal, thyrotoxicosis

patient's baseline and medical history may not be immediately available, however, it is useful to consider dementia, aphasia, and psychiatric decompensation in the initial approach to mental status change.

CAUSES OF MENTAL STATUS CHANGE

Causes of changes in mental status are numerous (Table 36.1). Indeed, almost any severe medical or surgical illness may cause delirium in a patient in the ICU, and many such patients have more

BOX 36.2 ■ Risk Factors for the Development of Delirium in the Intensive Care Unit

Dementia
Advanced age
Severe illness
Visual impairment
Dehydration
Electrolyte changes (see Table 36.E1)
Malnutrition
Trauma
Drug effects (see Table 37.1)
Infection (see Table 37.1)
Hip or other major bone fractures
Loss of circadian (day-night) clues
Sleep deprivation (see Chapter 44)
Sleep fragmentation (see Chapter 44)

See also Chapter 37 for details of the diagnosis and management of delirium in ICU patients.

than one risk factor (Box 36.2). In younger patients, drug abuse and alcohol withdrawal are the most common causes; in contrast, in the elderly, metabolic disturbances, infection (especially associated with severe sepsis), stroke, and iatrogenic drug effects predominate.

There is no single consensus categorization of the many and varied causes of change in mental status. The following five categories of etiologies form the basis for the systematic approach (Figure 36.1): (1) vital sign abnormalities; (2) infection; (3) vascular or structural central nervous system (CNS) abnormalities; (4) toxins, metabolic, and environmental factors; and (5) miscellaneous causes.

VITAL SIGN ABNORMALITIES

Virtually any vital sign abnormality may be associated with changes in mental status and in some cases may point to a singular cause. Brady- and tachyarrhythmias, hypo- and hypertension, hypoventilation, and oxygen desaturation all may worsen mental status and, if so, demand urgent intervention. An elevated respiratory rate may suggest any number of abnormalities, such as salicylate overdose, stroke, intracranial hemorrhage, early sepsis, severe pain or anxiety, or respiratory compensation for a metabolic acidosis. Hypothermia or hyperthermia may herald sepsis, indicate a thyroid abnormality, or, in the case of fever, suggest a drug or toxin reaction such as serotonin syndrome, neuroleptic malignant syndrome, or alcohol withdrawal (Chapters 31 and 57).

A "vital sign" not readily measured at the bedside, but just as important to aid in diagnosis, is $Paco_2$. CO_2 retention may be a particularly important contributor to a depressed level of consciousness, especially in patients with acute pulmonary pathology, obstructive or neuromuscular-related lung disease, obesity hypoventilation syndrome, or in those receiving opioids. Assessment of $Paco_2$ is particularly important in guiding the need for mechanical ventilation in patients with a change in mental status. As such, an arterial blood gas (ABG) should be strongly considered in the assessment of patients with changes in mental status, especially if a depressed level of consciousness is noted.

INFECTION

Almost any infection can contribute to a change in mental status, especially in the high risk patient population that inhabits the typical ICU. With the increasing prevalence of both elderly and immunosuppressed patients in ICUs, manifestations of infection can differ from classic descriptions. In some cases, change in mental status may be the initial sign. Infection may directly involve the central nervous system (CNS) (e.g., meningitis, encephalitis, brain abscess) or indirectly affect CNS function as a result of systemic response to infection (sepsis from pneumonia, urinary tract

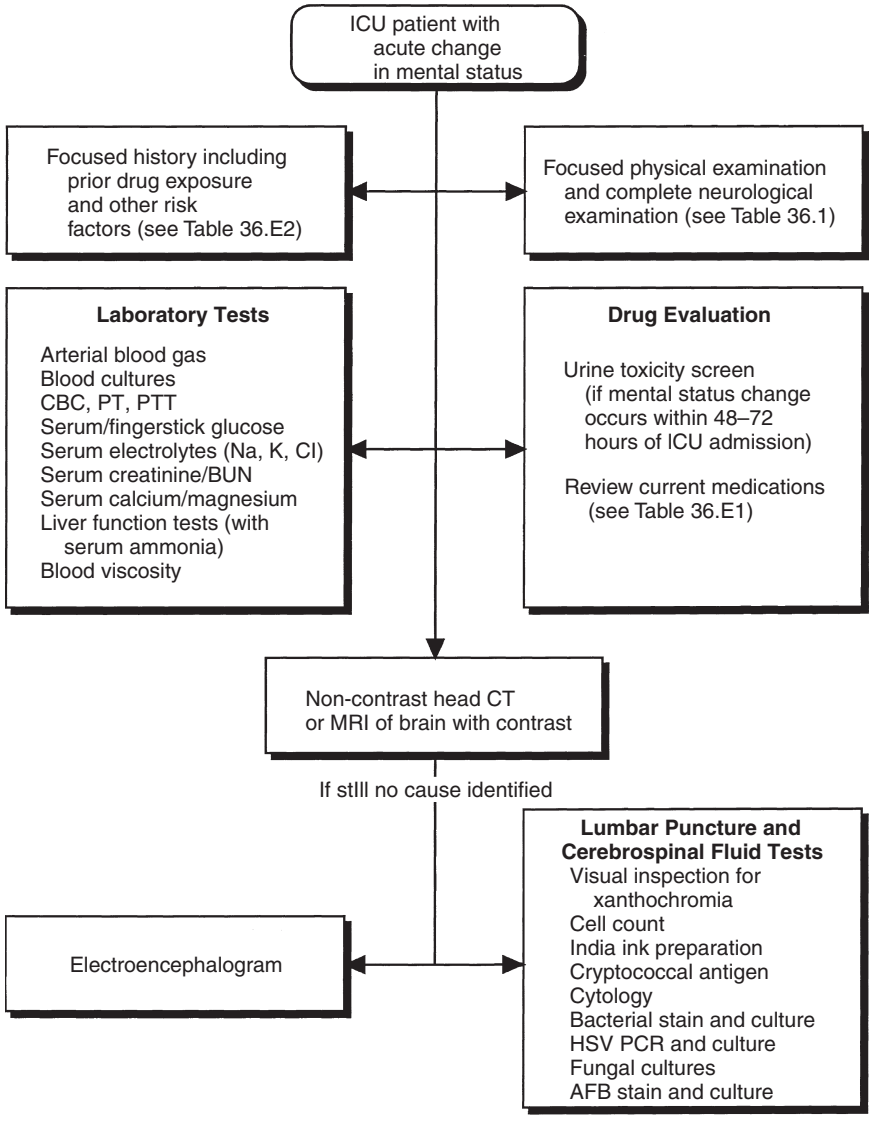


Figure 36.1 Flow diagram illustrating elements of the diagnostic evaluation for an acute change in mental status in a patient in the ICU (see text for details). AFB, acid-fast bacilli; BUN, blood urea nitrogen; CBC, complete blood count; CT, computed tomography; HSV PCR, herpes simplex virus polymerase chain reaction; MRI, magnetic resonance imaging; PT, prothrombin time; PTT, partial thromboplastin time. *Data from Slovis, C. Don't assume the intoxicated patient is just drunk. In Lawner BJ, Slovis CM, Fowler R, et al, eds. Avoiding Common Prehospital Errors. Philadelphia: Lippincott Williams & Wilkins, 2013, pp 361-363.*

infections, catheter-related bloodstream infections, etc.). The distinction is important because the former implies the potential need for brain imaging, lumbar puncture (LP), and empiric broad-spectrum antimicrobials that may not be indicated otherwise.

There are several key historical elements that can aid the clinician's approach to this issue. First, any recent neurosurgical intervention increases the likelihood of direct involvement of the

CNS by infection. Brain abscess, while uncommon, is also associated with recent dental, ear, and sinus infections and procedures. Second, immunosuppression heightens the risk of atypical CNS infections, such as those caused by *Listeria monocytogenes* or fungi, which may be either community-acquired or nosocomial. Third, the length of time since admission can give a clue as to the likelihood of bacterial meningitis and certain viral encephalitides. One small study in nonsurgical patients suggested that a lumbar puncture done to rule out CNS infection in patients whose symptoms (mental status change, fever, headache, or meningeal signs) arose > 48 hours after admission had a very low yield. Because of the size of the study and small numbers of immunosuppressed patients, only limited conclusions can be drawn. Nonetheless, nosocomial meningitis in the nonsurgical population is thought to be rare, and the study lends some weight to this idea.

Finally, the presence of an apparent alternative infectious explanation to mental status change (e.g., evident urosepsis in an elderly patient) may be sufficient to forego a further lumbar puncture unless it seems otherwise clinically indicated. However, clinical judgment should be used regarding the corresponding severity of infection and mental status change. Although the preceding elements may help in making workup decisions, they will ultimately depend on the patient's entire clinical picture, including individualized risks of the interventions (see also Chapter 64 on acute CNS infections).

STRUCTURAL OR VASCULAR CNS ABNORMALITIES

Elevations of intracranial pressure (mass, hydrocephalus, hemorrhage, edema), ischemic strokes, CNS vascular abnormalities (vasculitis, microangiopathy of thrombocytic thrombocytopenic purpura [TTP], or malaria), and seizures may all manifest as a change in mental status. Mass or hemorrhage may be suspected on the basis of history (metastatic cancer, new-onset seizure, coagulopathy, trauma). Any acute stroke may transiently result in confusion, which typically clears within 48 hours, though peri-infarct edema may worsen over several days. Strokes involving the right middle cerebral artery and certain other structures may cause a more prolonged change in mental status.

Posterior reversible encephalopathy syndrome (PRES) is an increasingly recognized phenomenon that may result from the failure of cerebral autoregulation and focal endothelial damage, with resultant blood-brain barrier breakdown and vasogenic edema. It is characterized clinically by acute encephalopathy, headache, vomiting, and visual impairment and may result in seizures. The classic associated condition is severe hypertension, but many conditions put patients at risk for PRES with mild or no elevation in blood pressure (Table 36.E1). Early recognition and management of hypertension and seizures are key, as delayed therapy may lead to irreversible damage to the involved areas of the brain.

Both seizures and their treatment are potential causes of changes in mental status. After generalized or complex partial seizures, patients often are confused for minutes to hours. Occasionally, patients in nonconvulsive status epilepticus may appear confused without other seizure manifestations (Chapter 70). Many anticonvulsant medications can also induce changes in mental status because of their sedative properties.

The issues of mental status changes in patients with traumatic brain injury or postoperative vascular or craniotomy require more tailored approaches and are addressed separately (see Chapter 89 for craniotomy, Chapter 92 on vascular surgery, and Chapter 99 on head trauma).

TOXINS AND METABOLIC AND ENDOCRINE DISORDERS

By far the largest category in number, many of these disorders are potentially life threatening or may cause permanent damage, and their early identification is critical. Toxins can be thought of

as including medications (taken as prescribed and in overdose), drugs of abuse, drug withdrawal syndromes, and environmental toxins.

Medications work in an additive fashion, and a combination of medications may result in an acute confusional state when an individual drug alone would not. Drugs with anticholinergic properties, including over-the-counter cold preparations, antihistamines, tricyclic antidepressants, and neuroleptic agents, are frequent offenders. Other important and commonly used medications to consider include opioids, benzodiazepines, and nonbenzodiazepine sleep medications (e.g., diphenhydramine). Elderly patients are particularly susceptible because of lengthy medication lists, underlying dementia, and less efficient drug metabolism and clearance.

More dramatic syndromes may be seen with certain medications. Neuroleptic malignant syndrome (neuroleptics), serotonin syndrome, and malignant hyperthermia (anesthetics, succinylcholine) are characterized by changes in mental status accompanied by high fever and rigidity (though milder forms may be seen). Salicylate overdose may result in mental status changes ranging from mild confusion to unresponsiveness, whereas acetaminophen toxicity may impair mental status because of acute liver failure and consequent cerebral edema. High-dose corticosteroids may induce an acute toxic psychosis. Methemoglobinemia is an uncommon cause of mental status change that may be precipitated by a number of medications (see Table 62.2 in Chapter 62) and characteristically presents with oxygen desaturation despite adequate Pao_2. It is easily detectable by co-oximetry.

Many drugs of abuse—including barbiturates, benzodiazepines, amphetamines, cocaine, and alcohol—can cause changes in mental status via direct effect or drug withdrawal. The classic alcohol withdrawal syndrome delirium tremens begins 72 to 96 hours after alcohol withdrawal. It is characterized by profound agitation, tremulousness, diaphoresis, tachycardia, fever, and visual hallucinations (see Chapter 31 for details related to alcohol withdrawal syndrome).

Numerous electrolyte disturbances may present with mental status changes (see Table 36.E1). Hypoglycemia is a critically important etiology to address quickly, as appropriate correction can prevent permanent neurologic insult. The most important nutritional metabolic disturbance is *thiamine deficiency*. Thiamine must be given prophylactically to alcoholics to prevent precipitating Wernicke encephalopathy with the administration of glucose, though deficiency should be suspected in any malnourished patient. Hepatic and renal dysfunction is quite common in the ICU population and may cause encephalopathy independently or in the setting of a precipitating factor. In the patient with cirrhosis, the possibility of spontaneous bacterial peritonitis should be entertained in this setting. Thyroid and adrenal abnormalities may cause a spectrum of changes in mental status.

Many environmental toxins may result in altered mental status. In general, conditions related to carbon monoxide, cyanide, or organophosphate poisoning will be recognized in the emergency department, but the intensivist should still consider these diagnoses in newly admitted patients with mental status abnormalities of unclear etiology. In-hospital development of cyanide toxicity may occur with nitroprusside use.

MISCELLANEOUS CAUSES

Many other disturbances occasionally produce change in mental status. For example, in some studies, 50% of elderly patients admitted with hip fractures experienced delirium, which was likely multifactorial in origin.

The "ICU syndrome" is a delirium that may result from the multiple stressors in the ICU, including sleep deprivation, immobilization, unfamiliarity, fear, and sensory overstimulation or deprivation (see Chapter 37 on delirium and Chapter 44 on sleep disturbances for more details). Patients recovering from surgery often experience acute delirium (see Chapter 37), typically developing around the third postoperative day and lasting several days. As previously mentioned, psychiatric conditions may mimic a true mental status change.

TABLE 36.E1 ■ **Differential Diagnosis: Acute Mental Status Change in Patients in the Intensive Care Unit***

Vital Sign Abnormalities
Hypotension and shock
Hypertensive encephalopathy
Tachy- and bradyarrhythmias
Hypo-, hyperthermia
Acute hypercapnia
Hypoxemia
Infections
CNS
Meningitis
Encephalitis
Brain abscess
Non-CNS
Severe sepsis or septic shock
Urinary tract infections (especially elderly)
Structural or Vascular CNS Abnormalities
Intracranial hemorrhage
Mass lesion or hydrocephalus
Acute ischemic stroke (any location for first 48 hours)
Posterior reversible encephalopathy syndrome (PRES)
Hypertensive encephalopathy
Preeclampsia/eclampsia/HELLP
Calcineurin inhibitors and other immunosuppressants
TTP/HUS
Others (e.g., liver failure)
Other vasculopathies
CNS vasculitis
Malaria
Leukemic blast crisis with leukostasis
Dural venous sinus thrombosis (headache prominent)
Seizure-related
Paraneoplastic syndrome
Demyelinating disease
Toxins, Metabolic and Endocrine Disorders
Medications
Opioids (systemic or neuraxial)
Anticholinergic agents
Benzodiazepines and other hypnotics
Neuroleptics
Serotonergic medications
Corticosteroids
Antiepileptic drugs
Salicylate, lidocaine, or digitalis toxicity
Baclofen withdrawal

Continued

TABLE 36.E1 ■ **Differential Diagnosis: Acute Mental Status Change in Patients in the Intensive Care Unit*** (Continued)

Drugs of Abuse (and withdrawal)
Stimulants (cocaine, amphetamine)
Ethanol
Methanol, ethylene glycol
PCP
Electrolyte Disorders
Hypo-, hypernatremia
Hypo-, hypercalcemia
Hypo-, hyperphosphatemia
Hypermagnesemia
Metabolic and Endocrine Disorders
Hypo-, hyperglycemia
Wernicke's encephalopathy
Hepatic encephalopathy
Uremia
Hypo-, hyperthyroidism
Hypo-, hyperadrenalism
Environmental Toxins
Carbon monoxide
Cyanide
Organophosphates
Heavy metals
Miscellaneous
Air embolism, amniotic fluid embolism
Major long bone fractures (with fat emboli syndrome)
Delirium ("ICU syndrome") (see Chapter 37)
Perioperative causes (see Chapter 37)
Disseminated intravascular coagulation
Psychiatric decompensation
Dementia

*Based on the organizational schema of XXX

CNS, central nervous system; HELLP, hemolysis, elevated liver function tests, low platelets; HUS, hemolytic uremic syndrome; PCP, phencyclidine; TTP, thrombocytopenic purpura.

Clinical Approach to Change in Mental Status

DIAGNOSIS AND INITIAL MANAGEMENT

Figure 36.1 shows one systematic approach to the ICU patient with a change in mental status. Establishing a time line of events and changes, as well as determining the patient's baseline mental functioning, is critical to establishing that a change in mental status has occurred. When this information can be gathered from chart documentation or by verbal report from family members or a transferring medical team, it can be very useful in focusing the proposed approach. Patient age, medical history, and time since hospital admission also play key roles in prioritizing workup.

The acute management of mental status change starts with assessing level of consciousness, ABCs (airway, breathing, and circulation), and vital signs. The addition of "NTG" (naloxone, thiamine, glucose) to the ABC mnemonic may serve as a useful reminder of common, easily treatable causes of mental status change. Empiric administration to all patients of the so-called coma cocktail, however, is not recommended. The potentially CNS-toxic effects of a dextrose bolus in the setting of stroke or impending cardiac arrest, in particular, mandate that administration be guided by clinical suspicion and rapid bedside glucose determination. Bedside measurements by fingersticks have been shown to be inaccurate in critically ill patients with hypoglycemia, so low-normal bedside values may warrant treatment, and verification with venous blood analysis is key. Naloxone and thiamine may be considered based on history and risk factors. The naloxone dose should be reduced if used in opioid-tolerant patients. Intravenous thiamine has shown a very low incidence of side effects and avoids the drawback of unreliable absorption with oral administration. Of note, the utility of the benzodiazepine antagonist flumazenil, sometimes included in the "coma cocktail," is highly limited in the ICU. There is unclear benefit to reversing isolated mild benzodiazepine overdose, and flumazenil increases risk of seizure in those with tricyclic antidepressant co-ingestion or those having received long-term sedation with benzodiazepines or with benzodiazepine drug dependence.

Following these initial steps, a thorough neurologic examination is of utmost importance. In the responsive patient, the exam may be used to rapidly assess for motor or sensory deficits, cranial nerve abnormalities, abnormalities of speech and vision, and asterixis. In the poorly responsive or uncooperative patient, the neurologic exam remains indispensable but a greater emphasis is placed on obtainable signs. Particular attention should be paid to pupils (and funduscopic exam, if possible); differences in withdrawal to pain between right and left; corneal, gag, cough, and other reflexes; the presence of decerebrate or decorticate posturing; and muscle tone (rigidity being a useful finding to narrow the differential). Although certain systemic phenomena (e.g., hypoglycemia) have been shown to present with focal exam findings, a new focal finding on exam increases the suspicion for a primary CNS abnormality and elevates the priority of expeditious imaging or electroencephalography (EEG).

Decisions regarding the timing and necessity of CNS imaging depend on patient risk factors, neurologic exam findings, likelihood of alternative diagnoses, and the risks of transport outside of the ICU (unless bedside computed tomography [CT] scanning is available). In most cases outside of known direct neurologic insult, waiting for preliminary lab results (such as blood gas results) and assessing the response to therapeutic measures that act quickly (such as dextrose) are reasonable actions to take before making a decision about imaging. Magnetic resonance imaging (MRI) is superior for detecting acute ischemic stroke, posterior fossa pathology, and vasculopathy including PRES. MRI may be considered in patients who are more stable with a high likelihood of these conditions. In practice, however, CT scanning without IV contrast may be more useful in the acute setting given its availability and capacity for rapidly identifying acute life-threatening processes such as hemorrhage, edema, and herniation.

The EEG is useful not only for identifying specific causes of delirium, such as a toxic encephalopathy caused by liver failure, but also for differentiating delirium from dementia or psychiatric

abnormalities. EEG changes are *always* present in delirium. Generalized slowing and disorganization are the most common changes, and specific patterns may suggest specific causes. EEG is also the only test that can confirm suspected nonconvulsive status epilepticus (NCSE). Good outcomes studies are not available to dictate the use of emergent EEG in all cases of mental status change. Clinical suspicion, neurologic consultation, and availability must be the guides for determining the use and timing of EEG.

Lumbar puncture should be performed when the cause of mental status change remains uncertain or in patients with features suggestive of CNS infection (see the previous discussion; also see Chapter 64 on acute CNS infections). The lumbar puncture should, however, usually be preceded by a brain imaging study, given the difficulty in ruling out increased intracranial pressure or mass effect in the posterior compartment in this patient population.

The importance of serial assessment cannot be stressed enough. Tracking ongoing changes in level of consciousness and cognition, in the context of diagnostic test results, contributes enormously to the clinician's ability to draw conclusions about etiology.

TREATMENT

Once the cause or causes of the change in mental status are identified, specific therapy should be directed at reversing or eliminating them. If the delirium is severe or persistent, however, additional treatments may be needed. In all cases, the sensory environment should be controlled. Sensory overstimulation or deprivation should be avoided by limiting ambient noise and visitation or by providing a radio or television set, eyeglasses, and hearing aid if a hearing disorder is present. The room should include a calendar, clock, family picture, and some personal items. Frequent family visits should be encouraged, and a full-time bedside companion may be needed. A regimen to promote good sleep hygiene should be initiated (Chapter 44).

Pharmacologic treatment should be employed only when the patient's behavior is dangerous, interferes with medical care, or causes the patient severe distress (see Chapters 5, 37, and 44 on treating distress and agitation, delirium, and sleep disturbances). Haloperidol and lorazepam are commonly employed medications. These drugs should be started at the lowest possible dose. Physical restraints should be avoided when possible because they often seem to aggravate the problem.

PROGNOSIS

Outcomes of mental status change depend heavily on underlying etiology and the rapidity of recognition and appropriate treatment. Underscoring the link between medical illness and mental status, hospital mortality rates in patients with delirium have ranged from 25% to 33%, with elderly patients potentially being at higher risk. Resolution tends to follow improvement of medical illness, with some deficits lasting days to weeks or even much longer.

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CHAPTER 37

Delirium in the Intensive Care Unit: Diagnosis and Treatment

David R. Janz ■ E. Wesley Ely

Delirium is defined as an *acute brain dysfunction* with a set of characteristic clinical features (Box 37.1). Delirium occurs in 50% to 80% of patients in intensive care units (ICUs). Although causality has not been established, delirium in ICU patients is associated with longer hospital stays, new cognitive impairment at discharge and often long-term postdischarge, and an increased risk of mortality after adjusting for possible confounding factors.

Despite its well-documented status as a problem for ICU patients, the pathophysiology of delirium in ICU patients remains poorly understood. Causes of delirium in ICU patients include a combination of neuroanatomic factors, the use of sedatives or analgesia, sleep deprivation and fragmentation, possible sepsis (or SIRS, systemic inflammatory response syndrome) and metabolic derangement, an imbalance of neurotransmitter release, and possible genetic factors. Commonly used medications in the ICU, including benzodiazepines and opioids, are well-known risk factors for the development of delirium. Imbalance in neurotransmitters such as acetylcholine, gamma-aminobutyric acid (GABA), glutamate, serotonin, and norepinephrine have all, to some degree, been implicated in the development of delirium. The presence of the apolipoprotein E4 polymorphism (ApoE4) in ICU patients has been associated with a longer duration of delirium on the order of 2 days.

Diagnosis

According to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), the clinical features of delirium consist of disturbances of consciousness and attention that have an acute onset, are dynamic, and are thought to be related to a medical condition.

Although various methods have been previously used for the recognition of delirium in the ICU, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) is currently the most widely used method (Figure 37.1 and Figure 37.E1). CAM-ICU encompasses all aspects of the traditional definition of delirium; allows for the assessment of nonverbal patients; and has a sensitivity between 93% and 100%, a specificity between 98% and 100%, and excellent interrater reliability. In addition, it can be used for serial bedside monitoring by clinicians and takes ~2 minutes to complete with minimal training. It can even be used to assess patients who are intubated or who have baseline dementia or severe depression. The CAM-ICU worksheet guides the practitioner through these steps and allows for objective documentation of changes in delirium from day to day (Figure 37.E2).

As the CAM-ICU worksheet (Figure 37.1) shows, one should first evaluate the patient for degree of sedation. This is best accomplished by using the Richmond Agitation-Sedation Scale (RASS) (see Table 5.1 in Chapter 5). Quantifying sedation levels by means of the RASS not only allows clear goals to be set for the amount of sedative needed but also allows the ICU practitioner

Additional online-only material indicated by icon.

BOX 37.1 ■ Clinical Criteria for Making a Diagnosis of Delirium in ICU Patients*

Criteria #	*Description*
1.	Acute change in mental status (or fluctuating mental status) AND
2.	Inattention AND
3.	Disorganized thinking OR
4.	Change in level of consciousness

*See text for details.
Delirium = Presence of criteria 1 + 2 + (3 or 4).
Adapted from Ely EW, Inouye SK, Bernard GR, et al: Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 286:2703-2710, 2001.

an objective and reliable scale to monitor the fluctuations in a patient's level of arousal, the first component in the CAM-ICU assessment. If the patient's RASS score has changed since a previous assessment or there is an acute change in mental status, the *first* feature of delirium is considered to be present.

Once an acute change from baseline or fluctuation in mental status is determined to be present, the *second* feature of delirium, inattention, can be assessed using the Letters Attention Test (see Figure 37.1). This consists of having the patient squeeze the examiner's hand when the examiner says certain letters aloud. If the patient is unable to perform this test, a set of pictures is also included in the CAM-ICU (www.ICUdelirium.org) to assess for inattention.

Patients can be assessed for the *third* feature of delirium, *disorganized thinking,* by being asked a series of questions that require the patient to be attentive and have clarity of thought. These questions are combined with simple commands, which further assess the patient's ability to comprehend, process information, and act appropriately. If disorganized thinking is *not* present, the *fourth* feature of delirium, *altered level of consciousness*, can be assessed by determining a patient's RASS score. If the patient has a RASS other than 0, this feature would be considered to be present.

Treatment

NONPHARMACOLOGIC PREVENTIVE MEASURES

Nonpharmacologic preventive measures aimed at some of the multiple possible causes can reduce the risk of delirium in ICU patients. These include frequent orientation by caregivers, early mobilization, sleep protocols including lights on during daylight hours and off at night, removal of restraints and catheters in a safe and timely manner, and minimizing unnecessary noise (See Chapter 44). Also, the RASS can be used to set a target goal of sedation to reduce the practice of giving more sedatives or opioids than necessary to achieve the desired level (see Chapter 5). ICUs may have a sedation-analgesia protocol to use for intubated and ventilated patients (Figure 37.E3). Likewise, some ICUs may have a delirium-related protocol (Figure 37.E4).

NONPHARMACOLOGIC AND PHARMACOLOGIC TREATMENT INTERVENTIONS

Even with preventive measures, however, delirium in ICU patients still occurs and must be diagnosed and treated in a timely manner. The goal is to decrease the risk of injury to self or staff as

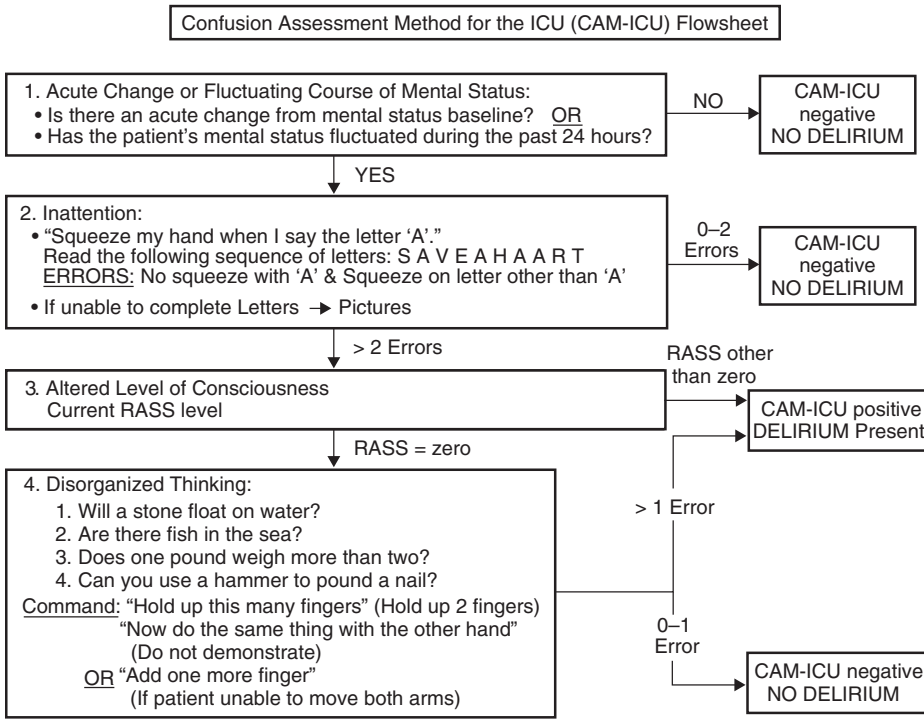
CAM-ICU Worksheet

Feature 1: Acute Onset or Fluctuating Course	Score	Check here if Present
Is the pt different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (i.e., RASS), GCS, or previous delirium assessment?	Either question Yes →	☐
Feature 2: Inattention		
Letters Attention Test (See training manual for alternate pictures) Directions: Say to the patient, "I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand." Read letters from the following letter list in a normal tone 3 seconds apart. S A V E A H A A R T Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."	Number of Errors > 2 →	☐
Feature 3: Altered Level of Consciousness		
Present if the Actual RASS score is anything other than alert and calm (zero)	RASS anything other than zero →	☐
Feature 4: Disorganized Thinking		
Yes/No Questions (See training manual for alternate set of questions) 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? Errors are counted when the patient incorrectly answers a question. Command Say to patient: "Hold up this many fingers" (hold 2 fingers in front of patient). "Now do the same thing with the other hand" (do not repeat number of fingers). If patient is unable to move both arms, for second part of command ask patient to "Add one more finger." An error is counted if patient is unable to complete the entire command.	Combined number of errors > 1 →	☐

Overall CAM-ICU Feature 1 plus 2 and either 3 or 4 present = CAM-ICU positive		
	Criteria Met →	☐ CAM-ICU Positive (Delirium Present)
	Criteria Not Met →	☐ CAM-ICU Negative (No Delirium)

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Figure 37.1 Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) worksheet to assess for the presence of delirium. RASS, Richmond Agitation-Sedation Scale (see Table 5.1 in Chapter 5); GCS, Glasgow Coma Scale. *(Copyright © 2002, E. Wesley Ely, MD, MPH, and Vanderbilt University, all rights reserved.)*



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Figure 37.E1 Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) flow sheet to assess for the presence of delirium. This is a shortened version of CAM-ICU worksheet (see Figure 37.1) (www.icudelerium.org). RASS, Richmond Agitation-Sedation Scale. (*Copyright © 2002, E. Wesley Ely, MD, MPH, and Vanderbilt University, all rights reserved.)*

PATIENT EVALUATION	Day 1	Day 2	Day 3	Day 4	Day 5
Altered level of consciousness* (A-E)					
If A or B do not complete patient evaluation for the period					
Inattention					
Disorientation					
Hallucination - delusion - psychosis					
Psychomotor agitation or retardation					
Inappropriate speech or mood					
Sleep/wake cycle disturbance					
Symptom fluctuation					
Total score (0–8)					

Level of consciousness*:		Score
	A: No response	None
	B: Response to intense and repeated stimulation (loud voice and pain)	None
	C: Response to mild or moderate stimulation	1
	D: Normal wakefulness	0
	E: Exaggerated response to normal stimulation	1

Scoring system:
The scale is completed based on information collected from each entire 8-hour shift or from the previous 24 hours.
Obvious manifestation of an item - 1 point. No manifestation of an item or no assessment possible - 0 point.
The score of each item is entered in the corresponding empty box and is 0 or 1.

1. Altered level of consciousness:
A) No response or B) the need for vigorous stimulation in order to obtain any response signified a severe alteration in the level of consciousness precluding evaluation. If there is coma (A) or stupor (B) most of the time period then a dash (-) is entered and there is no further evaluation during that period.
C) Drowsiness or requirement of a mild to moderate stimulation for a response implies an altered level of consciousness and scores 1 point.
D) Wakefulness or sleeping state that could easily be aroused is considered normal and scores no point.
E) Hypervigilance is rated as an abnormal level of consciousness and scores 1 point.

2. Inattention: Difficulty in following a conversation or instructions. Easily distracted by external stimuli Difficulty in shifting focuses. Any of these scores 1 point.

3. Disorientation: Any obvious mistake in time, place, or person scores 1 point.

4. Hallucination, delusion, or psychosis: The unequivocal clinical manifestation of hallucination or of behavior probably due to hallucination (e.g., trying to catch a non-existent object) or delusion. Gross impairment in reality testing. Any of these scores 1 point.

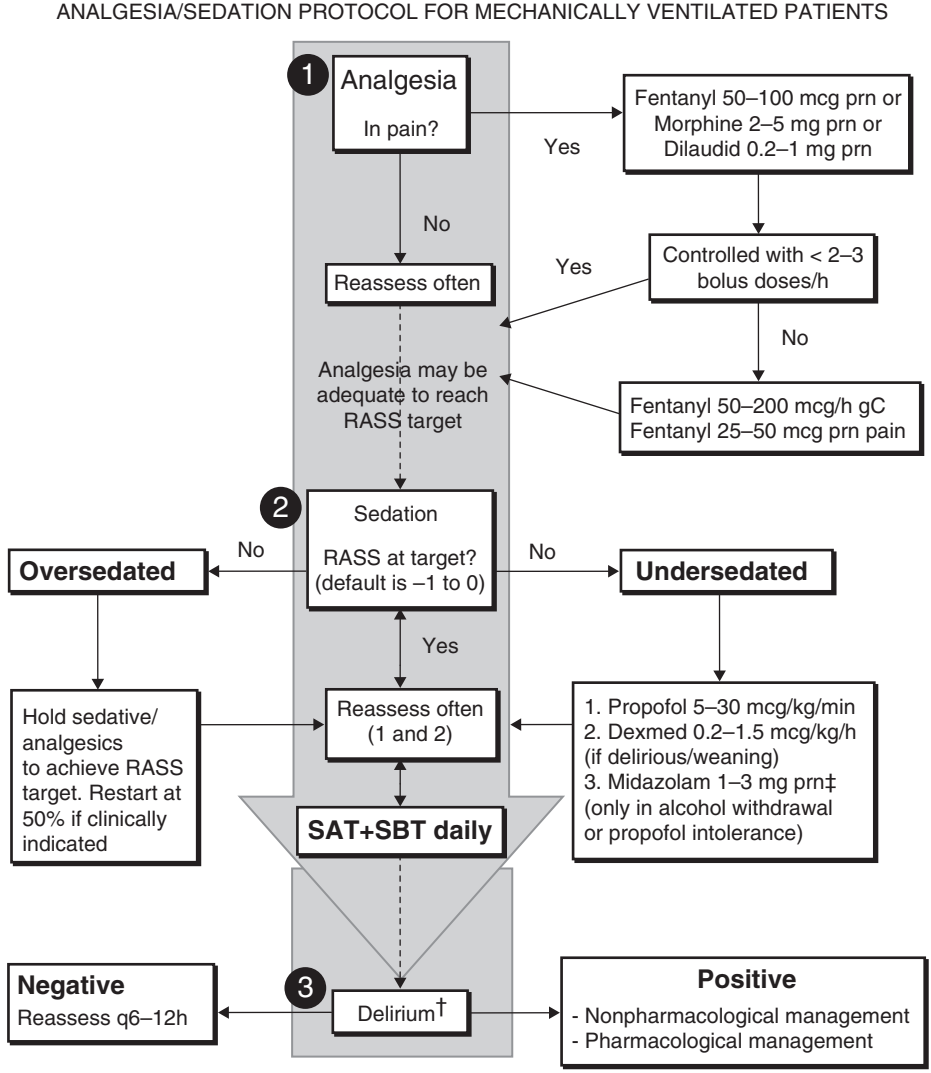
5. Psychomotor agitation or retardation: Hyperactivity requiring the use of additional sedative drugs or restraints in order to control potential dangerousness (e.g., pulling out iv lines, hitting staff). Hypoactivity or clinically noticeable psychomotor slowing. Any of these scores 1 point.

6. Inappropriate speech or mood: Inappropriate, disorganized, or incoherent speech. Inappropriate display of emotion related to events or situation. Any of these scores 1 point.

7. Sleep/wake cycle disturbance: Sleeping less than 4 hours or waking frequently at night (do not consider wakefulness initiated by medical staff or loud environment). Sleeping during most of the day. Any of these scores 1 point.

8. Symptom fluctuation: Fluctuation of the manifestation of any item or symptom over 24 hours (e.g., from one shift to another) scores 1 point.

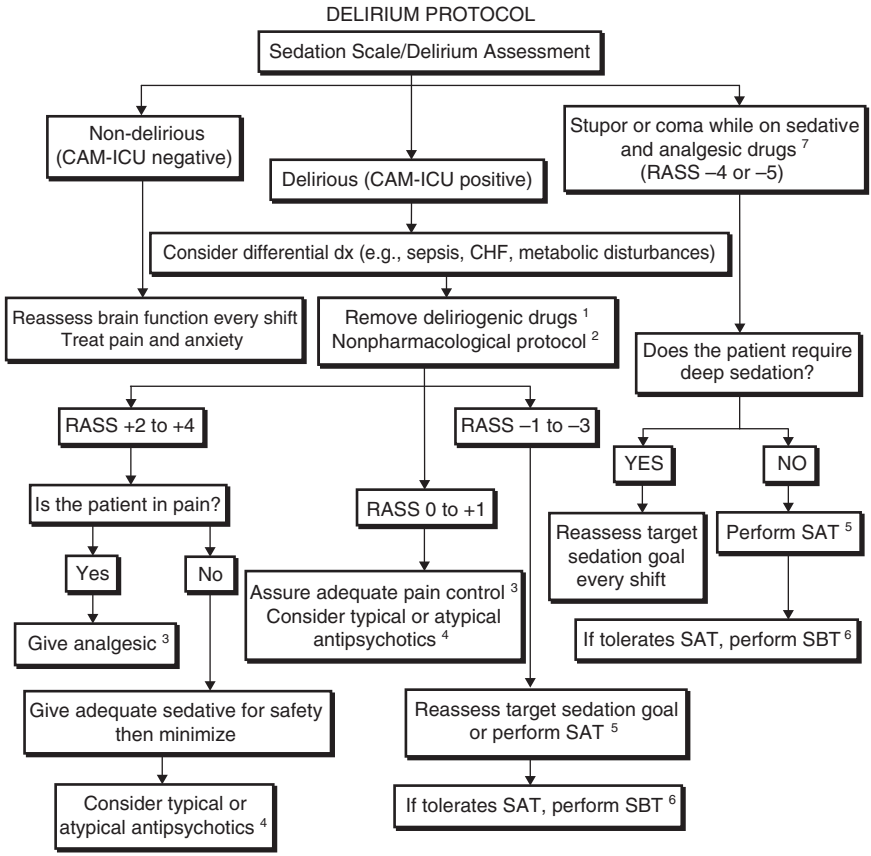
Figure 37.E2 Intensive Care Delirium Screening Checklist (ICDSC) (www.icudelerium.org). iv, intravenous. *(Copyright © 2002, E. Wesley Ely, MD, MPH, and Vanderbilt University, all rights reserved.)*



†Delirium diagnosed using the CAM-ICU or ICDSC
‡Midazolam 1–3 mg/h gC rarely if > 3 midazolam boluses/h, propofol intolerance or > 96 h propofol

© www.icudelirium.org

Figure 37.E3 Sample of protocol for managing sedation and analgesia in ICU patients who are intubated and receiving mechanical ventilation (www.icudelerium.org). prn, as needed; RASS, Richmond Agitation-Sedation Scale; gC, given as a continuous intravenous (iv) infusion; Dexmed, dexmedetomidine; SAT-SBT, spontaneous awakening trial-spontaneous breathing trial; q 6–12 h, every 6 to 12 hours; CAM-ICU, Confusion Assessment Method for the Intensive Care; ICDSC, Intensive Care Delirium Screening Checklist. *(Copyright © 2002, E. Wesley Ely, MD, MPH, and Vanderbilt University, all rights reserved.)*



1. Consider stopping or substituting for deliriogenic medications such as benzodiazepines, anticholinergic medications (metochlorpomide, H2 blockers, promethazine, diphenhydramine), steroids etc.
2. See nonpharmacological protocol – below
3. Analgesia – Adequate pain control may decrease delirium. Consider intermittent narcotics if feasible. Assess with objective tool.
4. Typical or atypical antipsychotics – While tapering or discontinuing sedatives, consider haloperidol 2 to 5 mg IV initially (0.5-2 mg in elderly) and then q6 hours. Guideline for max haloperidol dose is 20 mg/day due to ~60% D_2-receptor saturation. May also consider using any of the atypicals (e.g., olanzapine, quetiapine, risperidone, ziprasidone, or abilify). Discontinue if high fever, QTc prolongation, or drug-induced rigidity.
5. Spontaneous Awakening Trial (SAT) – Stop sedation or decrease infusion (especially benzodiazepines) to awaken patient as tolerated.
6. Spontaneous Breathing Trial (SBT) – CPAP trial if on ≤ 50% oxygen concentration and ≤ 8 PEEP and Sats 90% or higher
7. Sedatives and analgesics may include benzodiazepines, propofol, dexmedetomidine, fentanyl, or morphine

Nonpharmacological protocol[2]

Orientation
- Provide visual and hearing aids
- Encourage communication and reorient patient repetitively
- Have familiar objects from patient's home in the room
- Attempt consistency in nursing staff
- Allow television during day with daily news
- Non-verbal music

Environment
- Sleep hygiene: Lights off at night, on during day. Sleep aids (zolpidem, mirtazipine)?
- Control excess noise (staff, equipment, visitors) at night
- Ambulate or mobilize patient early and often

Clinical parameters
- Maintain systolic blood pressure > 90 mm Hg
- Maintain oxygen saturations > 90%
- Treat underlying metabolic derangements and infections

Last updated 01-30-07
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Figure 37.E4 Sample of protocol related to diagnosing, preventing, and managing delirium in ICU patients (www.icudelerium.org). Note: This file can be accessed at www.mc.vanderbilt.edu/icudelirium/overview.html. CAM-ICU, Confusion Assessment Method for the Intensive Care; RASS, Richmond Agitation-Sedation Scale; dx, diagnosis; CHF, congestive heart failure; SAT, spontaneous awakening trial; SBT, spontaneous breathing trial; IV, intravenous; q6, every 6; max, maximum; QTc, QT interval on electrocardiogram, corrected for heart rate; CPAP, continuous positive airway pressure; PEEP, positive end expiratory pressure; Sats, oxygen saturation by pulse oximetry. *(Copyright © 2002, E. Wesley Ely, MD, MPH, and Vanderbilt University, all rights reserved,* www.mc.vanderbilt.edu/icudelirium/docs/Delirium_Protocol_2001_30_07.pdf*.)*

a result of delirium-associated agitation and possibly the risk of long-term cognitive impairment and even death.

Using the CAM-ICU allows ICU practitioners to monitor central nervous system (CNS) functioning in managing patients with delirium. With CAM-ICU, they can target a level of sedation to objectively track the effects of any intervention. In addition, the nonpharmacologic, preventive measures previously described are just as important in the treatment of delirium as they are in prevention.

The first step in the pharmacologic management of delirium is a thorough review of the patient's current medications, with particular attention paid to sedatives, especially benzodiazepines, opioids, and anticholinergic medications. Often, these medications are added to treat agitation and subsequently cause a paradoxical worsening of the patient's delirium. Although sedation and analgesia are often needed in the ICU, a goal-directed sedation using the RASS should be used for accurate and consistent dosing and to help avoid overuse of these medications (see Chapter 5 and Figure 37.E3).

As of 2012, no drug has been approved by the Food and Drug Administration (FDA) for the treatment of delirium, but clinicians have used a variety of neuroleptic agents for this purpose. The Society of Critical Care Medicine has recommended the dopamine receptor antagonist, haloperidol, in the management of ICU patients with delirium. However, the data supporting this recommendation are predominantly anecdotal. Other antipsychotics, including olanzapine, risperidol, and quetiapine, have also been used for this indication, but, likewise, they have not been well studied in controlled clinical trials.

Future directions in the prevention and treatment of delirium in ICU patients are likely to inform the choice of sedatives and how they're used in patients receiving mechanical ventilation. Lorazepam, midazolam, and continuous infusion of sedatives (versus intermittent bolus dosing) have all been shown to be independent risk factors for the development of delirium in the ICU. These may induce an early transition to delirium by acting on the GABA receptors in the CNS and cause alterations in the levels of potentially deliriogenic neurotransmitters, such as dopamine, serotonin, acetylcholine, norepinephrine, and glutamate.

As examples of the type of clinical trials needed, Jakob et al in 2012 reported results of two clinical trials that compared two traditional sedatives to dexmedetomidine, a sedative and alpha-2 adrenergic agonist, for sedation in ICU patients. The first study compared the use of dexmedetomidine to midazolam and found that the incidence of neurocognitive disorders, including delirium, was similar in both study groups, whereas the second study found that the use of dexmedetomidine was associated with fewer neurocognitive disorders than the use of propofol.

See Chapter 5 and online materials related to spontaneous awakening trials (SATs) and spontaneous breathing trials (SBTs). Patients receiving continuous or intermittent intravenous (IV) infusions of sedatives should undergo daily interruption of these to determine if they are still required to manage the patient. This practice, referred to by some as "sedation stops" or SATs, in combination with daily SBTs should help to reduce the incidence and prevalence of delirium and possibly decrease the overall mortality of ventilated patients in the ICU (Figure 37.E5).

An SAT can generally be performed safely on patients unless they:

1) are receiving sedatives for active seizures or alcohol withdrawal,
2) are receiving increasing doses of sedatives due to ongoing agitation,
3) currently require neuromuscular blocking agents,
4) have had myocardial ischemia in the past 24 hours, or
5) have evidence of increased intracranial pressure.

The trial itself consists of a 4-hour interruption of sedatives, while the patients are closely monitored by ICU staff for failure criteria that consist of:

1) sustained anxiety, agitation, or pain,
2) a respiratory rate of ≥ 35 breaths per minute for 5 minutes or longer,

3) acute cardiac arrhythmia, or
4) two or more signs of respiratory distress, including tachycardia, bradycardia, use of accessory muscles of respiration, paradoxical abdominal movements, diaphoresis, or marked dyspnea.

If a patient exhibits any one of these failure criteria, sedative medications can be restarted at half of the previous dose and titrated up as needed. The patient should continue to be screened daily with the criteria previously stated to determine if she or he is an appropriate candidate for an SAT. Patients who pass the SAT should go on to be evaluated for an SBT, as ventilator and sedative weaning are inseparable in the management of the ventilated ICU patient.

Unfortunately, and despite the evidence showing the benefit of SATs and the risks associated with continuous IV infusion of sedatives without interruption, less than half of the ICU practitioners throughout the world have incorporated this information into their practices.

Conclusion

Data regarding the morbidity and mortality associated with delirium in the ICU are currently more robust and informative than results describing the possible interventions to prevent and treat delirium. However, this should not deter the practitioner from developing a protocol for the management of the delirious ICU patient and to achieve goal-directed sedation (e.g., Figures 37.E3 and 37.E4). As more data are generated from future studies regarding the pathophysiology and pharmacologic treatment of ICU delirium, protocols can be revised to incorporate these findings.

An annotated bibliography can be found at www.expertconsult.com.

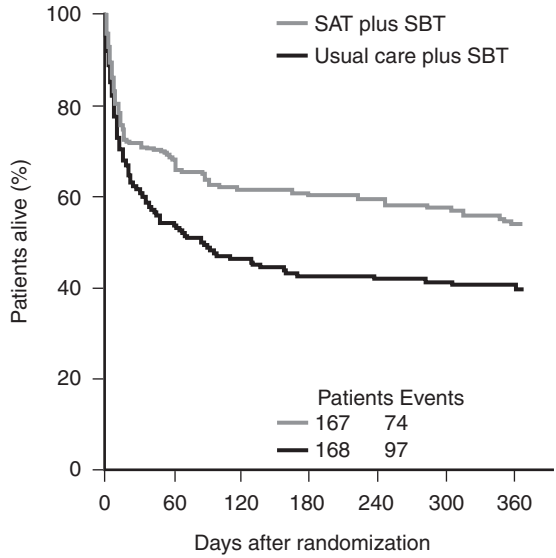


Figure 37.E5 Survival plots in patients who underwent a spontaneous awakening trial (SAT) paired with spontaneous breathing trial (SBT) (n = 167) compared to those who had spontaneous breathing trials alone (n = 168) when added to usual care. "Events" represent deaths. *(From Girard TD, Kress JP, Fuchs BD, et al: Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care [Awakening and Breathing Controlled trial]: a randomized controlled trial. Lancet 371: 126-134, 2008.)*

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CHAPTER 38

Diarrhea Developing in the Intensive Care Unit Patient

Paul Menard-Katcher ■ Gary R. Lichtenstein

Diarrhea is an important nosocomial disorder in hospitalized patients and occurs frequently in the intensive care unit (ICU). It has potentially debilitating consequences in these patients, including (1) decreased absorption of enterally administered medications and nutrition, (2) perineal and sacral skin ulcers with secondary superinfection, and (3) abdominal discomfort and the urge to defecate. Severe diarrhea can also cause intravascular volume depletion with its associated electrolyte abnormalities.

The incidence of diarrhea in the ICU is difficult to estimate, partly because of a lack of standard definitions of diarrhea. Health care workers use a variety of criteria to define diarrhea yet may not agree on the precise definition. Nevertheless, diarrhea has been estimated to occur in 14% to 30% of ICU patients. Diarrhea is defined as an increase in the fluidity, volume, and frequency of daily stool output. Typically, frequent stooling (greater than three to five bowel movements daily), stool volume output greater than 250 mL (or > 200 g in weight) per day, or soft/liquid stool is considered diarrhea for an adult.

Pathophysiology

Four major mechanisms can produce diarrhea: (1) secretory, (2) osmotic, (3) inflammatory, and (4) motility related (Table 38.1).

SECRETORY DIARRHEA

Active chloride secretion is the basic mechanism leading to secretory diarrhea. There are many known stimuli, including toxins, peptides, amines, and derivatives of arachidonic acid. The majority of these substances exert their action through intracellular mediators that stimulate active chloride secretion. The secreted chloride drives the retention of water in the gastrointestinal lumen leading to more liquid stools. Secretory diarrhea occurs even when the patient fasts because the secretory process is independent of enteral intake or the absorptive process (see Table 38.1). Active secretion of chloride anion creates an osmotic gradient in favor of moving water passively

TABLE 38.1 ■ **Major Types of Diarrhea, Examples, and Their Response to Fasting**

TYPE	EXAMPLE	RESPONSE TO FASTING
Secretory	Medications	None
Osmotic	Tube feedings	Resolves within 1 day
Inflammatory	*Clostridium difficile* toxin	Decreased volume
Altered intestinal motility	Small bowel bacterial overgrowth	Decreased volume

from plasma and interstitial space into the intestinal lumen. The osmolality of secretory diarrhea should be nearly iso-osmolar to plasma. This is reflected in the calculation of a fecal osmotic gap, which should be < 50 mOsm/kg in patients who have secretory diarrhea (Figure 38.2).

OSMOTIC DIARRHEA

An osmotic agent causing diarrhea is (1) soluble in water, (2) cannot be absorbed by the small intestine, or (3) may be metabolized by bacteria and converted to substances with smaller molecular weight in the distal intestine. On a per gram basis, a smaller molecular weight substance is a more effective osmotic agent than is a larger molecular weight substance. Osmotic diarrhea is the result of consuming nonabsorbable solutes by mouth or by nasogastric or nasoenteral tube. Thus, this type of diarrhea resolves once the osmotic load is eliminated—that is, after the patient is fasting (see Table 38.1). Because nonelectrolytes cause water retention in cases of osmotic diarrhea, the measured osmolality of the stool will differ (be higher than) from the osmolality of plasma. This will be reflected in the calculation of a fecal osmotic gap, which is typically > 125 mOsm/kg in osmotic diarrhea (Figure 38.2).

INFLAMMATORY DIARRHEA

Inflammatory (leaky membrane) diarrhea is usually associated with a damaged intestinal lining. Exudation via the damaged mucosa plus a decrease in absorption is the underlying mechanism. There are several clinical characteristics of leaky membrane diarrhea, including (1) mucosal damage that can be detected by endoscopy, (2) the presence of fecal leukocytes, (3) diarrhea that persists after fasting, and (4) diarrhea that often worsens after feeding (see Table 38.1).

MOTILITY-RELATED DIARRHEA

Decreased Motility

Gastrointestinal motility disorders such as progressive systemic sclerosis (scleroderma), diabetes mellitus, and chronic idiopathic intestinal pseudo-obstruction result in less effective clearance of bacteria from the intestine. Under these conditions, chronic small bowel bacterial overgrowth can occur. Although both anaerobes and aerobes overgrow, anaerobes produce most of the clinical problems. Deconjugation of bile salts by bacterial enzymes results in free bile acids in the proximal small intestine. Bile acids not only are toxic to mucosal cells but also can promote secretion. Both effects can cause diarrhea. In addition, impaired micelle formation resulting from reduced conjugated bile salt concentrations may cause fat malabsorption and steatorrhea. Unconjugated bile salts, bacterial infection, or fatty acids may induce malabsorption because of mucosal damage. Protein malnutrition may be exacerbated because proteins are catabolized by bacteria, and transluminal transport of amino acids and peptides may be decreased because of mucosal defects.

Increased Motility

Motility disturbances (such as postgastrectomy dumping syndrome) provide an example of increased motility of the small intestine relevant to the ICU population. This condition typically results in a decreased contact time of chyme with the absorptive surface areas.

Differential Diagnosis (Box 38.1)

ANTIBIOTIC-ASSOCIATED DIARRHEA

Antibiotic-associated diarrhea is frequently seen in patients in the ICU. Diarrhea may occur in up to 25% of patients receiving antibiotics. Antibiotic therapy predisposes the patient to

BOX 38.1 ■ Common Causes of Diarrhea in the ICU Patient

Antibiotic-associated diarrhea
Clostridium difficile toxin–related diarrhea
Drugs (see Box 38.2)
Enteral feeding–related diarrhea
Fecal impaction
Hypoalbuminemia
Fecal incontinence
Intestinal ischemia
Intestinal pseudo-obstruction
Lactose ingestion in a lactase-deficient individual

the development of at least two separate types of diarrhea: (1) osmotic diarrhea caused by altered colonic salvage of carbohydrates and (2) secretory diarrhea caused by *Clostridium (C.) difficile* toxin. Administration of oral or systemic antibiotics reduces the normal competitive flora, impairs colonic fermentation of carbohydrates, and increases the risk for the development of *C. difficile* strains. In patients with antibiotic-associated diarrhea (without *C. difficile* toxin), ingested carbohydrate that is unabsorbed in the small intestine enters the colon. There, it is not metabolized as normally occurs and can induce an osmotic diarrhea. Stool studies are typically normal in these individuals, and diarrhea resolves once the offending antibiotics are discontinued.

However, when an individual patient acquires diarrhea after the antibiotics are discontinued, one should suspect the development of *C. difficile*–related diarrhea. One third of the cases of *C. difficile*–related diarrhea occur *after* the antibiotics have been discontinued. It may be several weeks or longer between discontinuing antibiotics and the onset of the diarrhea. *C. difficile* is the pathogen in one third of cases of antibiotic-induced diarrhea. However, it is also present in many hospitalized patients with diarrhea unrelated to *C. difficile* toxin. Those who harbor the organism without the demonstration of symptoms are not at increased risk for the development of subsequent clinical illness, for example, pseudomembranous colitis or colonic perforation. However, they are capable of transmitting the organism to other patients through person-to-person contact and environmental contamination. In addition to antibiotic use, there are other risk factors for the development of *C. difficile*–related diarrhea including treatment in the ICU setting, proton-pump inhibitor therapy, and enteral feeding.

INTESTINAL ISCHEMIA

Intestinal ischemia is another cause of diarrhea in patients in the ICU. Risk factors include hypotension, hypoxemia, or sepsis. Ischemic colitis often presents with an abrupt onset of lower abdominal cramping, rectal bleeding, vomiting, and fever. The finding of fecal leukocytes indicates colonic involvement. Individuals with underlying atherosclerotic disease are especially vulnerable, as are those who have undergone an abdominal aortic aneurysm repair (during which the inferior mesenteric artery may be compromised) (see Chapter 92). Ischemic colitis may also result from vasculitis, a ruptured abdominal aneurysm, collagen vascular disease (e.g., systemic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, scleroderma), or colorectal cancer. The clinical presentation may vary from mild to severe diarrhea, with or without substantial abdominal discomfort. Ischemia involving the small bowel—that is, mesenteric ischemia—is a more serious problem than is ischemic colitis because of its higher associated mortality.

DIARRHEA-RELATED TO ENTERAL FEEDING

Another cause of diarrhea occurring in the ICU is enteral feeding because of poor tolerance to the constituents of enteral feeding formulas. A number of causes have been proposed, including a high osmolality of the solution (e.g., up to 690 mOsm/kg in some preparations), high rate of delivery, bacterial contamination of the feeding solution, malabsorption caused by partial villous atrophy of small bowel mucosa from prolonged fasting, previous malabsorption, and motility alterations with rapid intestinal transit.

DRUG-RELATED DIARRHEA

Many medications given alone or in combination may result in diarrhea. Medications suspended in sorbitol may cause profuse diarrhea—for example, greater than 1 L/day. This diarrhea is osmotic in nature and thus it resolves on discontinuation of the medication. The amount of sorbitol is not specified on labels of elixirs because it is considered to be an inactive ingredient. Elixirs of acetaminophen, furosemide, and metoclopramide are common medications that may contain sorbitol. In this type of drug-related diarrhea there is no evidence of inflammation, fecal leukocytes or blood in the stool, and the patient is afebrile in the prototypic case. Many drugs may cause diarrhea in hospitalized patients (Box 38.2).

Lactose intolerance is common in the general population and occurs in about 10% to 15% of individuals. Other populations have an even higher prevalence for this disorder—for example, it is as high as 60% to 70% in African Americans, Jews, Hispanics, Southern Europeans, and East Asians, and as high as 90% in Native Americans. Diarrhea occurs when a lactase-deficient individual ingests products containing lactose. Many medications (and foods) contain lactose because it is often used as a binder in certain medications. When such medications are given to patients in the ICU who have acquired temporary lactase deficiency because of fasting, diarrhea may result.

BOX 38.2 ■ Selected Medications Associated with Diarrhea in Hospitalized Patients

Antihypertensive medications (angiotensin-converting enzyme inhibitors)
Antineoplastic agents
Cholinergic drugs (glaucoma eye drops, bladder stimulants)
Cholinesterase inhibitors
Colchicine
Digitalis
Diuretics (furosemide, thiazides)
Gold preparations
Lactulose
Laxatives with phenolphthalein, anthraquinones, senna, aloe, ricinoleic acid (castor oil), bisacodyl
Magnesium-containing medications (antacids, $Mg(OH)_2$, milk of magnesia)
Mesalamine derivatives (Asacol, olsalazine, sulfasalazine, Pentasa, Lialda, Apriso, Canasa, and Rowasa)
Para-aminosalicylic acid
Prokinetic agents (metoclopramide)
Prostaglandin analog (misoprostol)
Quinidine, quinine
Sorbitol-containing products (elixirs, sugar-free gums or mints, or from pears, peaches, prunes, and orange juice)
Theophylline
Thyroid hormone

OTHER CAUSES OF DIARRHEA

Fecal impaction is a common cause of diarrhea in hospitalized or institutionalized patients and may occur in patients admitted to the ICU for other reasons. This disorder tends to occur more commonly in patients who have dementia or psychosis. A rectal examination and a flat plate of the abdomen should be performed to search for this disorder.

A *low serum albumin* level may be an independent risk factor for the development of diarrhea in the ICU setting. Some report that patients in the ICU with an albumin level of less than 2.5 g/dL consistently experience diarrhea when given full-strength tube feedings. In contrast, patients with a serum albumin level greater than or equal to 2.6 g/dL do not experience diarrhea under the same conditions. Hypoalbuminemia may predispose the patient to the development of diarrhea by several mechanisms, including decreased submucosal oncotic pressure and mucosal edema in the intestinal tract. The latter is more likely to occur in individuals who experience hypoalbuminemia in association with a hypercatabolic state. Hypoalbuminemia itself does not always lead to diarrhea because many individuals with nephrotic syndrome and other causes of hypoalbuminemia never acquire diarrhea.

Incontinence, defined as the involuntary release of rectal and bladder contents, may result in a clinical situation that is difficult to differentiate from diarrhea. It is thus termed *pseudodiarrhea.* It is associated with the release of solid feces. This may occur alone or in association with another cause of diarrhea. A digital rectal examination can estimate the rectal tone as well as the patient's ability to generate a rectal squeeze response. In individuals with this disorder, the stool weight is less than 200 g daily. Incontinence may also result from anal fistulas and fissures, tears from childbirth, diabetic neuropathy, trauma, anal intercourse, or neuromuscular diseases.

Diagnostic Evaluation

In the evaluation of diarrhea in the patient in the ICU, the first determination to make is whether or not the patient actually has diarrhea. An accurate description of the diarrhea is helpful for appropriate diagnosis and treatment. In particular, one should ascertain the duration of the suspected diarrhea, the stool volume, color, consistency, and relationship to feedings. Also, it is important to identify any underlying illnesses, travel history, systemic symptoms, and current medications. As even health practitioners may not agree on the characteristics of diarrhea, visual and descriptive aids have been developed to standardize definitions of diarrhea.

The patient's *history* can help differentiate small bowel from large bowel diarrhea. Classically, patients with diarrhea that has a small bowel cause have high-volume diarrhea (several liters daily) with periumbilical cramping. The stools may be greasy or watery or contain particles of undigested food. In large bowel–related diarrhea, the patient classically passes small volumes of diarrhea, frequently with mucus and occasionally with blood. The patient may have a sense of urgency or tenesmus. If abdominal pain is present, it is typically localized to the lower abdomen, pelvis, or sacral region. The finding of blood in the diarrhea (either macroscopic or occult) should suggest inflammatory, vascular, neoplastic, or infectious causes.

The *physical examination* should evaluate for the presence of intravascular volume depletion and a rash suggestive of a vasculitis. Several findings may be of help in the evaluation of an individual with diarrhea, including the presence of a goiter, an abdominal bruit, arthritis, uveitis, peripheral neuropathy, orthostatic hypotension, perianal disease (fistula, abscess, mass), or fecal impaction.

Several *diagnostic tests* have proved useful in evaluating the patient with diarrhea in the ICU (Figure 38.1). They include a complete blood count with differential, serum electrolytes, serum blood urea nitrogen, and serum creatinine determinations. A chemistry profile and urinalysis may also help assess for the presence of systemic diseases. Several tests on the stool itself can help to determine the cause of the diarrheal disorder.

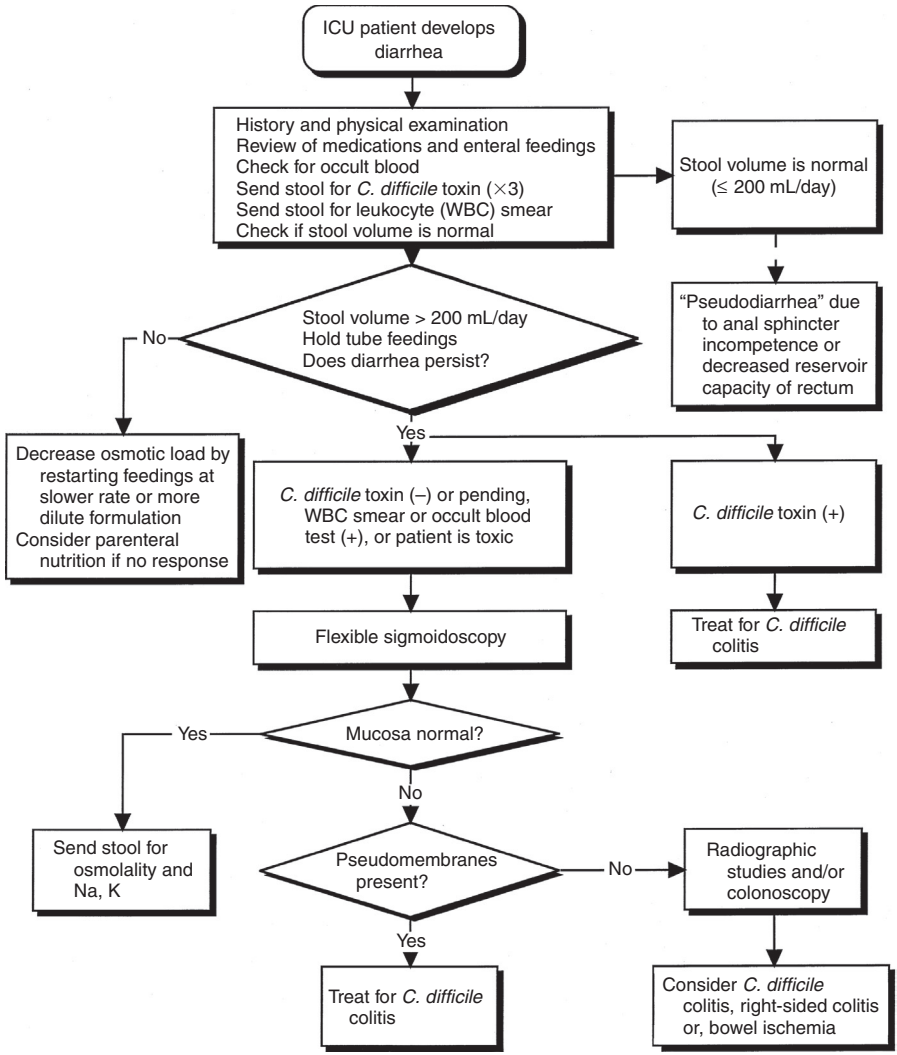


Figure 38.1 Schematic flow diagram for evaluation of diarrhea in the ICU patient. WBC, white blood cell; Na, sodium; K, potassium.

Fecal leukocytes are found in several infectious conditions. Typically, fecal leukocytes are present in *Shigella, Campylobacter,* and invasive *Escherichia coli,* whereas they may be present variably in *Salmonella, Yersinia enterocolitica, Vibrio parahaemolyticus, C. difficile*, or antibiotic-associated diarrhea. They may also be present in inflammatory bowel disease or ischemic colitis. One should note that it would be unusual for an infectious bacterial cause (other than *C. difficile*) to be responsible for *nosocomial* diarrhea.

The *absence of fecal leukocytes* suggests a nonbacterial, non-invasive process involving the intestinal tract. Examples include viral infections, giardiasis, and medication-associated diarrhea. However, the absence of fecal leukocytes (false-negative results) does not exclude the possibility of ischemia or other disorders in which they typically are present.

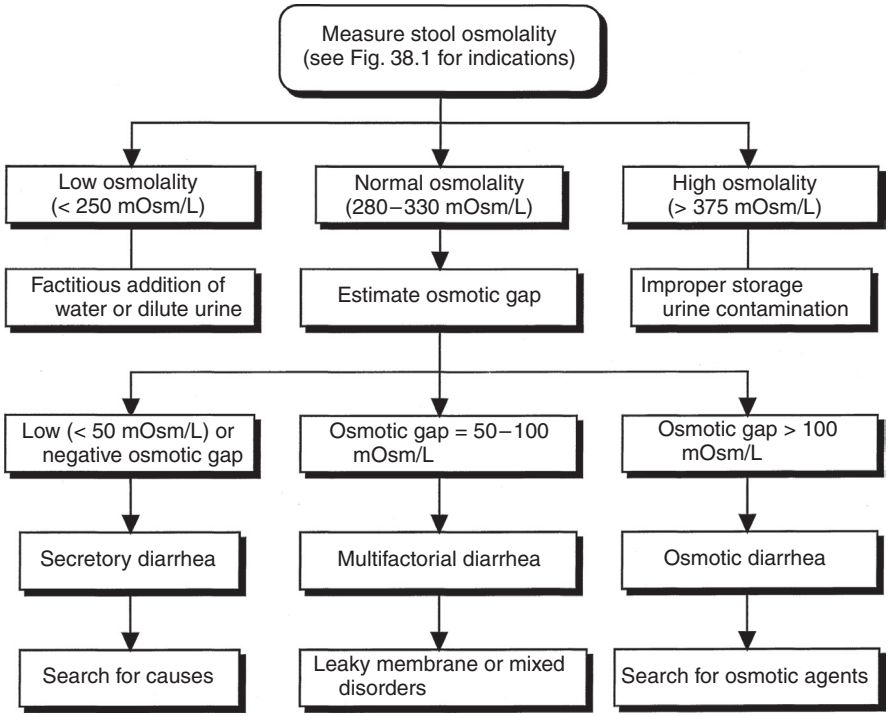


Figure 38.2 Flow diagram for measuring stool osmolality in the evaluation of diarrhea in the ICU patient. The osmotic gap equals 290 minus the calculated stool osmolality. Calculated stool osmolality = 2 × {stool [Na] + stool [K]} where [Na] is sodium concentration (mEq/L) and [K] is potassium concentration (mEq/L).

The presence of *gross or occult blood* in the stool is suggestive of severe mucosal inflammation, a neoplasm, ischemic bowel disease, radiation enteritis, or amebiasis. One should remember that upper gastrointestinal mucosal disease—for example, peptic ulcer disease—may cause stools to be positive for occult blood (i.e., false-positive results).

Measurement of *stool osmolality* can help differentiate osmotic from secretory diarrhea (Figure 38.2). In addition, high stool sodium concentration (> 90 mmol/L) suggests secretory diarrhea (or osmotic diarrhea caused by ingestion of Na_2SO_4 or Na_2PO_4), whereas a low stool sodium concentration (< 60 mmol/L) suggests osmotic diarrhea. In some cases, a fecal osmotic gap may be a useful diagnostic calculation. The formula to calculate the fecal osmotic gap is 290 − 2([Na+] + [K+]); 290 is the approximate osmolality of stool in the distal intestine where it equilibrates with serum osmolality. The sum of stool potassium and sodium is added and then multiplied by 2 to account for associated anions. In osmotic diarrhea, the fecal osmotic gap is normally > 125 mOsm/kg, as nonelectrolytes account for the majority of stool osmolality. In secretory diarrhea, the fecal osmotic gap is usually < 50 mOsm/kg, as secreted electrolytes are responsible for the stool osmolality.

Bacterial pathogens (other than *C. difficile*) and *parasitic organisms* may cause disease that results in patients being admitted to the ICU. However, such infections would rarely cause diarrhea with an onset more than 2 days after hospitalization (especially when the patient had no symptoms before admission). Under such conditions, do *not* request stool cultures for bacterial pathogens but instead send stool to be evaluated for the presence of *C. difficile.* Currently the most commonly used test for detecting *C. difficile* infection is the enzyme immunoassay (EIA) for toxin A or B.

Although the sensitivity for the toxin A and/or B EIA is variable (31% to 99%), the role of other diagnostic tests (e.g., polymerase chain reaction to amplify the genes that encode toxin production) remains uncertain and evolving. Endoscopy has a limited role in the diagnosis of *C. difficile* infection, in cases requiring a rapid diagnosis or presenting atypically (such as patients with ileus).

Flexible sigmoidoscopy is a helpful procedure and can be performed without any preparatory enemas or with normal saline enemas. During the test, stool samples can be obtained via suction if further testing is indicated. Sigmoidoscopy is especially helpful for evaluating patients in whom pseudomembranous colitis (highly suggestive of *C. difficile* infection) is suspected.

Radiographic studies may be helpful but usually are not necessary if the preceding studies have been performed. A plain radiograph of the abdomen may show thumbprinting suggestive of mucosal disease (e.g., inflammatory bowel disease or ischemic bowel disease). Computed tomography of the abdomen may show similar changes and help establish a specific diagnosis, such as ischemic bowel disease.

Management and Treatment

Treatment of diarrhea depends on its specific cause (see Box 38.1 and Figure 38.1). However, a careful review of medications (especially antibiotics, elixirs, and magnesium-containing antacids) and probable causes is recommended as the first step for all patients. A physical examination, including a rectal examination, should be performed to exclude an impaction and to search for occult blood.

In a patient receiving enteral nutrition in the ICU who experiences diarrhea, several strategies can help eliminate this as its cause. They include decreasing the rate of feeding, increasing the dilution of the feeding, or stopping the enteral feedings and changing to parenteral feeding temporarily if not contraindicated. The fecal osmotic gap in patients with an osmotic diarrhea resulting from enteral feedings is typically greater than 100 mOsm/kg (see Figure 38.2).

If *C. difficile* is suspected, patients should have stool samples tested for *C. difficile* toxin, as described above. However, if the patient appears toxic, urgently perform a sigmoidoscopy or colonoscopy to look for pseudomembranes. When searching for ischemia, one should look for occult blood in stool. Sigmoidoscopy, colonoscopy, or radiographic studies (computed tomography, barium studies, or plain abdominal radiographs) may be needed to search for changes of ischemia. If ischemia is found, one should maintain adequate blood flow and oxygen delivery to the gastrointestinal tract—that is, transfuse if necessary and increase cardiac output as well as decrease its metabolic demands by "resting" the bowel (fasting). Surgery is indicated in severe cases or in recurrent prolonged colonic disease. Mortality is high (exceeding 50%) for small bowel ischemia.

The treatment of infectious diarrhea is divided into several categories, including (1) symptomatic therapy (fluid and electrolyte replenishment and use of antidiarrheal agents) and (2) specific antimicrobial treatment. In all patients, the degree of intravascular volume depletion should be determined and patients rehydrated with intravenous fluids.

Although the preferred initial treatment for of *C. difficile* toxin–related diarrhea is metronidazole (500 mg orally every 8 hours for 7 to 14 days), this is not the recommendation in patients with severe or complicated infection who are common in the ICU setting. Severe infection occurs with a concomitant leukocytosis or evidence of renal insufficiency (serum creatinine > 1.5 × baseline); and treatment is recommended with vancomycin (125 mg orally 4 times daily for 10 to 14 days). Complicated *C. difficile* infection exists when there is associated hypotension, shock or ileus; in these cases, initial recommended therapy is vancomycin (500 mg enterally 4 times daily) AND metronidazole (500 mg intravenously every 8 hours). In uncomplicated patients with an ileus, intravenous metronidazole (500 mg every 8 hours for 10 to 14 days) is equally efficacious to oral administration; and can be administered in conjunction with rectal vancomycin, as well. Metronidazole should be the initial drug of choice for the treatment of mild to moderate *C. difficile* because

of the higher cost of treatment with vancomycin and concern that the overuse of vancomycin predisposes to resistant organisms, such as enterococci or staphylococci. When used, vancomycin is effective only when administered orally or via nasogastric tube; intravenous vancomycin is *ineffective*. Approximately 15% to 20% of patients relapse after treatment with vancomycin, which sometimes occurs 1 to 5 weeks after completion of therapy. Retesting for *C. difficile* toxin is the preferred method of diagnosis (or detection of pseudomembranes on flexible sigmoidoscopy or colonoscopy when necessary). Eradication of the toxin from the stool occurs in about 80% of individuals within 5 days of initiation of therapy using vancomycin. The use of agents to slow intestinal motility—for example, loperamide—should not be used in individuals who have diarrhea caused by *C. difficile* toxin. Their use in this disorder may precipitate toxic megacolon. Similarly, the use of opioids and anticholinergics is *not* recommended in these individuals. The use of probiotics has been examined in the treatment of *C. difficile*–related diarrhea, and at this time there does not appear to be definitive role for their use in treatment. One small study did reveal a benefit to the probiotic *Saccharomyces boulardii*; its use was associated with decreased recurrence of *C. difficile*–related diarrhea. Fecal transplantation is also being assessed for refractory cases.

Clinical Pearls and Pitfalls

The following imperatives can serve as general guidelines:

1. Look carefully at the medications that the patient is receiving, especially elixirs that may contain sorbitol.
2. Check stool for *C. difficile* toxin.
3. Perform a rectal examination to exclude impaction.
4. Assess for tube feeding–related diarrhea.
5. Look for complications of systemic diseases.
6. Look for evidence of ischemic bowel disease.
7. Avoid antimotility agents until diarrhea caused by *C. difficile* toxin is excluded.
8. Avoid empirical antibiotics to treat *C. difficile* unless indicated by demonstration of its toxin or the patient is toxic.

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This small comparative effectiveness trial showed that supplementing standard oral vancomycin therapy for C. difficile *colitis with fecal transplantation was more effective than vancomycin alone.*

CHAPTER 39

Electrolyte Disorders

F. Perry Wilson ■ Jeffrey S. Berns

Electrolyte disturbances are common among patients in intensive care units (ICUs). Anticipation and prompt recognition of these disorders are crucial skills for the physician providing care for critically ill patients. Appropriate treatment depends on an understanding of the underlying pathophysiologic processes, as well as an appreciation of the often complex and multisystem disorders affecting these patients. This chapter addresses electrolyte disorders of potassium, calcium, magnesium, and phosphorus. Separate chapters address acid-base disorders (Chapters 82 and 83) and disorders of water homeostasis and the serum sodium concentration (Chapter 84).

Potassium Disorders

Approximately 98% of total body potassium is intracellular, a balance that is maintained by the Na^+-K^+-ATPase and the influence of several hormones such as insulin and catecholamines. Most of the clinical effects of potassium disturbances are related to alterations of the cellular membrane potential that result from changes in the extracellular potassium concentration. The normal potassium concentration in extracellular serum ranges from 3.5 to 4.5 mmol/L. Because the cellular membrane potential is a function of the ratio of the intracellular to extracellular potassium concentration, and the intracellular potassium concentration is relatively constant in the range of 120 to 150 mmol/L, even relatively small changes in the extracellular potassium concentration can significantly alter the cellular membrane potential. Significant clinical consequences are rarely seen, however, unless the potassium concentration in the blood falls below 3 mmol/L (hypokalemia) or rises above 5.5 mmol/L (hyperkalemia).

HYPERKALEMIA

Box 39.1 lists common acute causes of hyperkalemia relevant to the ICU setting. Before pursuing a diagnosis of hyperkalemia, it is important to consider *pseudohyperkalemia,* when an elevation in measured serum potassium concentration is due to potassium movement out of cells into the serum during or after the blood specimen has been obtained. In pseudohyperkalemia, the true potassium concentration in blood and plasma is normal, but when measured in the serum by the clinical laboratory, an elevated value is reported. Major causes of pseudohyperkalemia include hemolysis resulting from mechanical trauma during venipuncture, severe thrombocytosis (> 400,000/mm^3) or leukocytosis (> 100,000/mm^3), repeated fist clenching during blood drawing (resulting from the release of potassium by exercising muscle), and, less commonly, hereditary spherocytosis and familial pseudohyperkalemia. Diagnosis of pseudohyperkalemia caused by the release of intracellular potassium from platelets or white blood cells within the specimen container can be made by obtaining a plasma (unclotted) potassium concentration, which is normally < 0.5 mmol/L lower than the serum potassium concentration.

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BOX 39.1 ■ Causes of Hyperkalemia

Pseudohyperkalemia

Excessive Potassium Intake

Dietary intake
Prescribed oral or intravenous supplementation

Shift from Intracellular Fluid (ICF) to Extracellular Fluid (ECF)

Exercise
Hyperkalemic periodic paralysis
Hypertonicity: hyperglycemia, mannitol, hypertonic saline
Insulin deficiency
Metabolic acidosis
Rhabdomyolysis, muscle ischemia-reperfusion (see Chapter 81)
Succinylcholine (see also Chapter 6)
Tumor lysis syndrome (see Chapter 81)

Reduced Potassium Excretion

Acute kidney injury
Chronic kidney disease
Adrenal (mineralocorticoid) deficiency/insufficiency
—Addison disease
—Heparin
—Nonsteroidal anti-inflammatory drugs (NSAIDs)
Renal tubule hyporesponsiveness/resistance to mineralocorticoids
—Chronic tubulointerstitial disease
—Hyperkalemic distal renal tubular acidosis (RTA) (Chapter 83)
—Hyporeninemic hypoaldosteronism
—Potassium-sparing diuretics, trimethoprim
—ACE inhibitors/angiotensin receptor blockers
—Calcineurin inhibitors (e.g., cyclosporine and tacrolimus)
—Urinary tract obstruction

Multiple factors are necessary to overcome the several autoregulatory mechanisms protective of the extracellular potassium concentration, in order to produce acute or chronic hyperkalemia. Homeostatic mechanisms maintain balance between intracellular and extracellular potassium (internal balance) and control renal (and to a much lesser extent gastrointestinal [GI] tract) potassium excretion (external balance) to prevent development of significant hyperkalemia even despite large increases in potassium intake. Consequently, clinically significant sustained hyperkalemia generally requires both disturbed internal balance and impaired renal excretion. Impaired adrenal function or impaired responsiveness to the effect of adrenal hormones, particularly aldosterone, is also often present, as a consequence of intrinsic adrenal gland disease or medications that inhibit aldosterone synthesis or interfere with the renin-angiotensin-aldosterone system (see Box 39.1).

Clinical Manifestations

Because of its critical role in establishing transmembrane potential, elevations in serum potassium concentration affect cardiac membrane potential and neuromuscular transmission with related clinical effects predominantly involving the myocardium and skeletal muscles. The earliest manifestation, usually seen when potassium concentration is above 5.5 to 6 mmol/L, is peaking of the T waves on the electrocardiogram (ECG) with shortening of the QT interval (Figure 39.E1*A*). More severe hyperkalemia (i.e., > 6 mEq/L) is first associated with prolongation of the PR interval and QRS complex duration. As the potassium concentration rises further,

the P wave may be lost entirely, the QRS complex widens further and merges with the T wave producing a "sine wave" pattern; ventricular fibrillation or ventricular standstill with cardiac arrest may occur (Figure 39.E1*B*). However, serum potassium concentration poorly correlates with observed ECG changes in hyperkalemia, and the effect of hyperkalemia on myocardium is influenced by acidosis, hyponatremia, and hypocalcemia, all of which increase the neuromuscular effects of hyperkalemia. Careful monitoring and prompt treatment of patients with even minor ECG findings are essential.

The most prominent neuromuscular effects of hyperkalemia are muscle weakness and fatigue; eventually paralysis occurs, usually seen only with severe hyperkalemia (> 8 mmol/L). Impairment of respiratory muscle function may also occur with severe hyperkalemia.

Treatment

Prompt reversal of hyperkalemia and prevention of its cardiac effects are necessary to mitigate the life-threatening nature of hyperkalemia-induced cardiac arrhythmias. In all hyperkalemic patients, excessive potassium intake in the diet, medications, and enteral or parenteral nutrition should be eliminated. If possible, discontinue medications that impair urinary potassium excretion (see Box 39.1). In the setting of the previous ECG or other neuromuscular manifestations, treatment should proceed in three phases.

1. **Stabilization of Cardiac Membrane Potential.** Calcium salts antagonize the cardiac effects of high extracellular potassium concentration through unclear mechanisms. They do not lower the serum potassium concentration. Intravenous (IV) administration of one 10-mL ampule of 10% *calcium gluconate* (1000 mg in 10 mL, which contains 4.65 mEq Ca^{++}) given over 2 to 3 minutes will typically reverse ECG manifestations of hyperkalemia within minutes. This dose can be repeated after 5 minutes if ECG abnormalities persist. Constant ECG monitoring is essential. *Calcium chloride* is sclerosing and should be avoided or given only via central venous access. Caution is necessary in patients taking digitalis, as hypercalcemia can provoke digitalis toxicity. If required, these patients should receive a slow IV infusion of calcium over 20 minutes.
2. **Shift of Potassium into Cells.** The movement of extracellular potassium into cells will lower the extracellular potassium concentration and allow time for initiating more definitive therapy aimed at reducing total body potassium. Insulin and beta-adrenergic agonists are the most potent and reliable agents used for this purpose; both work by stimulating the Na^+-K^+-ATPase.

Regular insulin (10 units as a rapid intravenous bolus) along with 50 mL of *50% dextrose* in patients who are not hyperglycemic (to prevent insulin-induced hypoglycemia) lowers the serum potassium concentration by 0.5 to 1 mmol/L, an effect that peaks at about 60 minutes and lasts for several hours.

Beta-agonists also stimulate the Na^+-K^+-ATPase and cellular potassium uptake. *Albuterol sulfate* 10 to 20 mg via nebulizer over 10 minutes (a dose 5 times higher than that used for asthma treatment) lowers serum potassium concentration within about 90 minutes and can lower the serum potassium concentration to an extent similar to insulin (i.e., ~0.5 to 1 mmol/L), although a response is seen less consistently than with insulin. Subcutaneous *terbutaline* (7 mcg/kg) can also be used with similar effect. Because of their cardiac effects, beta-agonists should not be used in patients with active ischemic coronary artery disease.

By buffering extracellular H^+ and raising blood pH, *sodium bicarbonate* given as 50 mL of 7.5% solution intravenously over several minutes can lead to an exchange of intracellular hydrogen for extracellular potassium. Intravenous sodium bicarbonate is not as effective as insulin or beta-agonists in lowering the serum potassium concentration, especially in the absence of severe acidosis, and risks volume overload and hypernatremia. In addition, the hypertonic nature of the solution will cause water movement from the intracellular to extracellular space, carrying via convection the intracellular potassium concentration of 120 meq/L, thus potentially *increasing* serum potassium concentration. As such, the use of IV sodium bicarbonate should be limited to patients with hyperkalemia and concomitant severe acidemia.

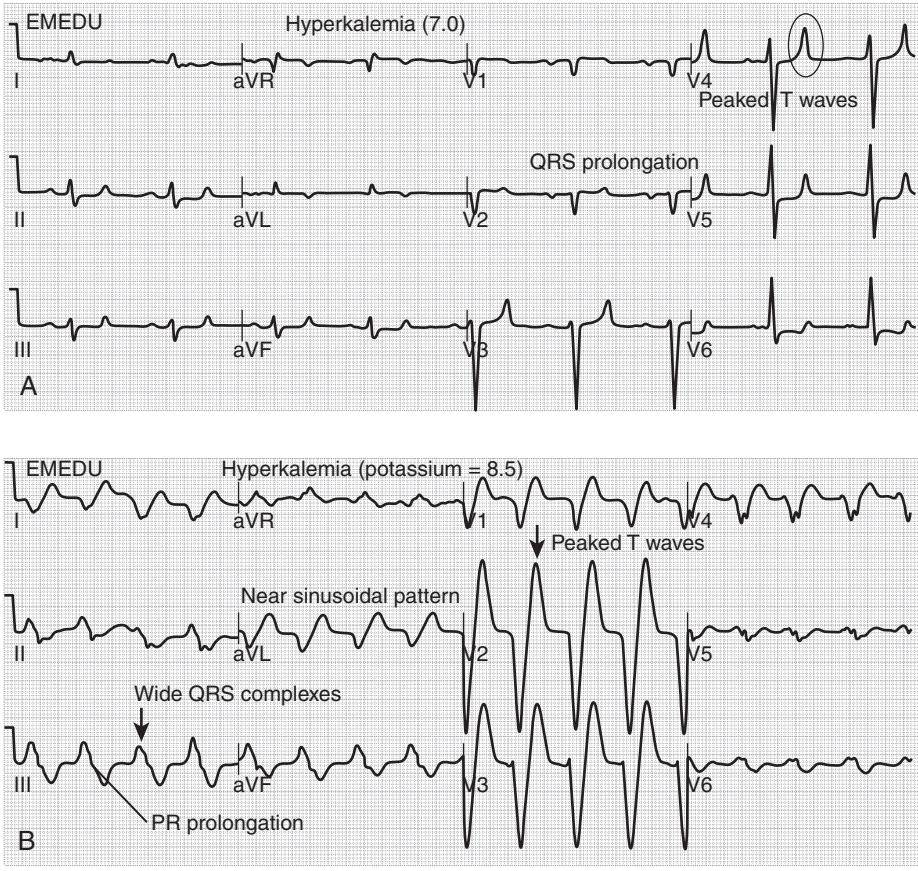


Figure 39.E1 ECG representing clinical manifestations of elevated potassium. **A,** Potassium concentration above 5.5 to 6 mmol/L leads to peaked T waves with shortening of the QT interval. **B,** As potassium concentration rises, the P wave may be lost entirely, and the QRS complex widens and mergers with the T wave, producing a sine wave.

3. Reduction of Total Body Potassium. Although these therapies will stave off cardiac disaster associated with acute hyperkalemia, only a reduction of total body potassium will prevent persistent hyperkalemia. With adequate renal function, treatment with a thiazide or loop diuretic (with supplemental IV fluid if needed) increases urinary excretion of potassium, although the extent and rate of potassium excretion with diuretics are neither consistent nor significant enough to be relied on for treatment of other than very mild acute hyperkalemia. Loop diuretics in particular can be useful in the prevention of chronic hyperkalemia.

The cation exchange resin *sodium polystyrene sulfonate* (SPS; *Kayexalate*) binds potassium (and to a lesser extent calcium and magnesium) in exchange for sodium when present in the lumen of the GI tract; each gram of SPS binds approximately 1 mmol of potassium and releases up to 2 mmol of sodium. SPS can be given orally or by retention enema. Because oral SPS tends to be constipating, 15 to 30 grams is usually administered in a 20% sorbitol solution to prevent constipation. Sorbitol also causes an osmotic diarrhea, which, independent of the SPS, can help to lower the serum potassium concentration. A powdered form that can be mixed with sorbitol or other liquids is also available. The dose can be repeated every 4 to 6 hours as necessary. Higher oral doses (60 g) can be used, but the sodium load must be considered in patients with advanced renal failure and heart failure. An enema of 30 to 60 grams of SPS mixed with tap water (*not* sorbitol) should be retained in the colon for at least 30 to 60 minutes and preferably up to 4 hours; this can be repeated in 2 to 4 hours if needed. Colonic necrosis has been reported in patients receiving SPS orally in sorbitol or by enema; this risk appears to be greatest in patients who have recently had abdominal surgery, so avoid SPS administration in these patients.

Hemodialysis will rapidly and definitively reduce total body potassium and is indicated if the more conservative measures described earlier are not successful. Dialysis is particularly likely to be necessary in patients with severe hyperkalemia that is associated with tissue breakdown (such as rhabdomyolysis or tumor lysis syndrome), acute kidney injury (especially if oliguric), and in patients with chronic end-stage renal disease who are already on dialysis. Hemodialysis can remove as much as 50 mmol of potassium per hour and lower the serum potassium concentration by 2 to 3 mmol/L or more within a few hours of starting the hemodialysis treatment. Remember that a serum potassium concentration obtained shortly after the completion of a hemodialysis treatment will be lower, often substantially, than one obtained a few hours later, as potassium moves from cells to the extracellular fluid compartment. The initial low postdialysis potassium concentration should not prompt potassium supplementation in patients dialyzed to treat hyperkalemia. Peritoneal dialysis and continuous renal replacement therapy are both less efficient at removing potassium than hemodialysis, but can be used in mild hyperkalemia.

HYPOKALEMIA

Hypokalemia can develop from an internal shift of potassium from the extracellular to intracellular spaces without a deficiency of total body potassium. More commonly, hypokalemia results from total body potassium deficits that can be in the range of several hundreds of mmol because of excessive losses via the GI tract, kidneys, or both, often exacerbated by inadequate oral intake. Box 39.2 lists important causes of hypokalemia (serum potassium concentration < 3.5 mmol/L) that are commonly seen in ICU patients. Hypokalemic patients with primarily extrarenal potassium losses and intact renal resorptive capacity should have daily urinary potassium excretion < 20 mmol and urinary potassium concentration < 10 mmol/L. Levels exceeding these values suggest at least some element of urinary potassium wasting.

Clinical Manifestations

Even though hyperkalemia has primarily neuromuscular and cardiac effects, hypokalemia has more varied effects impacting multiple organ systems, although patients with mild hypokalemia or hypokalemia that develops slowly may be asymptomatic.

BOX 39.2 ■ Causes of Hypokalemia

Inadequate Intake

Shift from Extracellular Fluid (ECF) to Intracellular Fluid (ICF)

Catecholamines, beta-receptor agonists, insulin
Hypokalemic periodic paralysis
Hypothermia
Respiratory and metabolic alkalosis

Excessive Excretion

Renal
—Amphotericin B, aminoglycosides
—Bartter's and Gitelman's syndromes
—Diuretics (loop or thiazides)
—Fanconi syndrome
—Hypomagnesemia
—Mineralocorticoid excess
—Poorly reabsorbable anions in urine
—Proximal renal tubular acidosis (RTA), distal RTA
—Saline diuresis
Gastrointestinal tract
—Diarrhea
—Laxative abuse
—Vomiting, nasogastric (NG) suction
Excessive sweating (rare)
Dialysis

Gastrointestinal symptoms include constipation that can progress to paralytic ileus, depending on the severity of the hypokalemia. Musculoskeletal effects range from mild generalized weakness, cramps, paresthesias, and myalgias with mild hypokalemia to loss of deep tendon reflexes, rhabdomyolysis, and skeletal and respiratory muscle paralysis at serum potassium concentration < 2 to 2.5 mmol/L. ECG changes include ST segment depression, reduced T-wave amplitude, and development of prominent U waves. Cardiac arrhythmias associated with hypokalemia include sinus bradycardia, paroxysmal tachycardia, atrioventricular blocks, premature atrial and ventricular beats, and ventricular tachycardia and fibrillation. Use of digitalis glycosides, concomitant cardiac ischemia, and hypomagnesemia potentiate the likelihood of hypokalemia-associated cardiac arrhythmias. Hypokalemia also impairs urinary concentrating ability with symptoms of nocturia and polyuria because of nephrogenic diabetes insipidus and increases renal ammoniagenesis, which can precipitate or worsen hepatic encephalopathy. It augments renal hydrogen ion (H^+) excretion, promoting development of metabolic alkalosis (Chapter 83). If long-standing and severe, hypokalemia can cause renal interstitial fibrosis, tubular atrophy, and renal cyst formation associated with reduced glomerular filtration rate and chronic kidney disease (CKD).

Treatment

Potassium repletion along with reversal of underlying and ongoing potassium losses is the mainstay of therapy for hypokalemia. Anticipate total body potassium deficits of at least 200 to 400 mmol in most patients with clinically significant hypokalemia. At serum potassium concentration < 2 mmol/L the deficit may exceed 600 to 800 mmol.

Take care during repletion of critically ill patients with long-standing hypokalemia, as they may not be able to rapidly shift administered potassium loads intracellularly. Overly aggressive

intravenous repletion can result in dangerous hyperkalemia. Therefore, oral or enteral repletion with 40 mmol of elemental potassium as *potassium chloride* capsules, tablets, or elixir (*potassium citrate* or *potassium bicarbonate* may be given in patients with metabolic acidosis) is safest for mild and moderate hypokalemia. Monitor the serum potassium concentration every 4 to 6 hours and administer repeat doses as needed until the potassium concentration normalizes and remains within the normal range. The serum potassium concentration can acutely rise by as much as 1.5 mmol/L after an oral dose of 60 meq but will typically subsequently decline because of cellular potassium uptake until the total body potassium deficit has been corrected.

When hypokalemia is severe or oral administration is contraindicated, IV *potassium chloride* can be given in concentrations of 20 to 60 mmol/L. Avoid higher concentrations, which can be painful and sclerosing to veins and be potentially dangerous if infused too rapidly. In patients who cannot tolerate large volumes of fluid, more concentrated solutions can be infused into a large central vein but not via catheters with their tips in the distal superior vena cava or right atrium, as direct delivery of high concentrations of potassium to the heart can cause serious arrhythmias. To prevent potentially fatal transient hyperkalemia, repletion should generally not exceed 10 to 20 mmol per hour although higher rates of infusion with continuous cardiac monitoring and frequent serum potassium concentration measurements may be necessary in patients with severe life-threatening hypokalemia. Clinicians should avoid the common tendency to underdose potassium repletion in patients with renal failure because of the concern of precipitating hyperkalemia. In these patients, frequent administration of small doses of potassium is advised with regular monitoring of the serum potassium concentration. Intravenous potassium should be given in saline rather than dextrose-containing fluids, as a glucose-induced increase in insulin release can shift potassium intracellularly, further decreasing its serum concentration. Supplemental *potassium phosphate* (15 to 30 mmol over 3 to 6 hours) can be used instead of KCl or other potassium salts in patients with hypokalemia and hypophosphatemia.

Hypokalemia can be accompanied by hypomagnesemia because of processes that cause both disorders as well as an effect of hypomagnesemia to induce urinary K^+ wasting. Correction of the hypomagnesemia will be necessary to reverse the hypokalemia.

Calcium Disorders

Normal calcium balance is maintained through a variety of hormonal actions and physiologic feedback loops. Cholecalciferol (vitamin D3), synthesized in sun-exposed skin and provided in the diet, is hydroxylated in the liver to 25-OH vitamin D and then in the kidneys to the primary active form of 1,25-$(OH)_2$ vitamin D; 1,25-$(OH)_2$ vitamin D acts to increase intestinal absorption of calcium and phosphate and to increase bone mineralization. The serum calcium concentration is tightly regulated by combined actions of 1,25-$(OH)_2$ vitamin D and parathyroid hormone (PTH) on the GI tract, bone, and kidneys.

Clinical laboratories report total serum calcium concentrations (normal range 9 to 10.5 mg/dL; 2.25 to 2.60 mmol/L). Approximately 45% of total serum calcium is protein bound, primarily to albumin, and about 10% is complexed with bicarbonate, phosphate, citrate, and other anions in the circulation. The remainder is the biologically active free, ionized serum calcium (normal range 4.5 to 5.3 mg/dL; 1.12 to 1.32 mmol/L). Although total serum calcium correlates well with ionized levels in healthy patients, several factors make this relationship less reliable in the ICU, particularly hypoalbuminemia and changes in blood pH. As a consequence, ionized calcium levels are best for diagnosing and managing calcium disorders in ICU settings.

Changes in the serum albumin concentration are associated with parallel changes in total serum calcium concentration. A commonly used approximation is that for each 1 g/dL decrease

in albumin concentration below 4.5, the total serum calcium would be expected to fall by 0.8 mg/dL. This relationship allows clinicians to estimate the "corrected" total serum calcium accounting for the presence of hypoalbuminemia. Systemic pH and other factors (serum phosphate concentration, PTH level) can also influence the ionized calcium concentration. Acidemia decreases calcium binding to albumin and increases the fraction of total calcium that is in the ionized form. Conversely, alkalemia decreases the ionized calcium concentration by increasing the binding of calcium to albumin. For instance, acute respiratory alkalosis causes the ionized calcium concentration to decline by approximately 0.16 mg/dL (0.04 mmol/L) for each 0.1 unit increase in pH. Direct measurement of ionized calcium is possible in most clinical laboratories and should be employed in any patient with signs or symptoms concerning for hyper- or hypocalcemia with a normal total serum calcium concentration and in patients in whom serum total calcium measurements may be unreliable because of the presence of factors mentioned previously.

HYPERCALCEMIA

Box 39.3 lists some of the more common causes of hypercalcemia relevant to the ICU setting. Asymptomatic or mildly symptomatic hypercalcemia, particularly if relatively chronic, is more likely to be due to hyperparathyroidism, whereas severe and acute hypercalcemia is more often a complication of underlying malignancy. Appropriate initial workup includes a careful review of the diet and medication list (prescription, over-the counter, vitamin and calcium supplements) as well as measurement of the intact PTH level. Further diagnosis should proceed according to the clinical presentation and may include measurement of serum phosphate, 25-(OH) vitamin D, 1,25-$(OH)_2$ vitamin D level, PTH-related protein, serum and urine protein electrophoreses, and evaluation for malignancy.

Clinical Manifestations

Symptoms of hypercalcemia vary depending on the rapidity of onset and severity of the hypercalcemia. Patients with mild to moderate hypercalcemia (serum calcium 11 to 14 mg/dL) may be asymptomatic or have nonspecific symptoms such as constipation, fatigue, depression, and

BOX 39.3 ■ Causes of Hypercalcemia

Excess parathyroid hormone (PTH) effect
—Primary hyperparathyroidism
—Secondary hyperparathyroidism (especially patients with chronic kidney disease taking calcium supplementation)
Granulomatous disease (local production of 1,25-$[OH]_2$ vitamin D)
Malignancy
—Local production of osteoclast stimulating cytokines
—Parathyroid hormone-related protein (PTH-RP) releasing tumors
—Tumor production of 1,25-$(OH)_2$ vitamin D
Increased bone turnover
—Prolonged immobilization (especially young patients)
—Thyrotoxicosis
Increased renal resorption
—Adrenal insufficiency
—Thiazide diuretics
Recovery postrhabdomyolysis (unclear mechanism)

anorexia. Other manifestations that may be present at these and higher serum calcium concentrations depending on the chronicity and severity of the hypercalcemia include polyuria and polydipsia resulting from nephrogenic diabetes insipidus and urinary sodium wasting, hypertension (unless volume contracted), nausea and vomiting, pancreatitis, peptic ulcer disease, lethargy, confusion, decreased cognitive function, psychosis, coma, acute kidney injury, and shortening of the QT interval and elevation of the ST segment on ECG.

Treatment

Patients with mild hypercalcemia (total serum calcium <12 mg/dL) who are asymptomatic or have only mild symptoms do not require urgent treatment. Patients with more severe hypercalcemia (total serum calcium > 13 to 14 mg/dL) and those with changes in mental status or with other significant symptoms regardless of serum calcium concentration require more immediate treatment. The overall approach to management of hypercalcemia includes inhibiting bone resorption, increasing urinary calcium excretion, and decreasing absorption of calcium from the GI tract. Hemodialysis may be necessary in patients with impaired kidney function.

The initial therapy for acute hypercalcemia is normal saline administration, as many patients are volume contracted because of impaired renal salt and water handling, anorexia, and vomiting. Correction of intravascular volume contraction with isotonic saline administration initiated at 200 to 300 mL/h and then adjusted to maintain a urine output of 100 to 150 mL/h will increase urinary calcium excretion. However, this usually suffices to correct only very mild hypercalcemia. Administration of loop diuretics may augment renal calcium excretion, but care must be taken to avoid further volume contraction and other electrolyte abnormalities. Do not use thiazide diuretics, which reduce urinary calcium excretion. Bisphosphonates inhibit bone resorption and are very useful for the initial management of malignancy-associated hypercalcemia.

These agents typically require several days for maximal lowering of the serum calcium concentration, so they are often given in conjunction with saline and other therapies. *Zoledronic acid* (4 mg IV) and *pamidronate* (60 to 90 mg IV; 30 mg in patients with estimated reduced glomerular filtration rate [GFR] < 20 mL/min) are the most commonly used bisphosphonates for treatment of hypercalcemia. *Calcitonin* also reduces bone resorption; it is usually administered at a dose of 4 international units (IU)/kg intramuscularly or subcutaneously every 12 hours, although doses up to 8 IU/kg every 6 hours have also been used. Calcitonin has a more rapid onset of action than the bisphosphonates, with a calcium-lowering effect beginning within 4 to 6 hours. Tachyphylaxis limits its effect after 24 to 48 hours, so it is most useful in conjunction with saline for acute management of hypercalcemia while awaiting the more delayed effect of bisphosphonates. Prednisone or other glucocorticoids may be useful in management of patients with hypercalcemia resulting from excess vitamin D levels, as they reduce calcitriol ($1,25\text{-}[OH]_2$ vitamin D) synthesis, or in cases of multiple myeloma. In patients with hypercalcemia due to parathyroid carcinoma or severe primary hyperparathyroidism, the calcimimetic *Cinacalcet* 30 to 90 mg orally may help to reduce PTH levels and improve hypercalcemia. Urgent parathyroidectomy may be necessary for the rare patient with parathyroid carcinoma or tertiary hyperparathyroidism.

In patients with severe hypercalcemia and advanced renal failure, hemodialysis with a low calcium dialysate concentration may be necessary. Low-calcium peritoneal dialysis may also be effective but will lower the serum calcium concentration more slowly.

HYPOCALCEMIA

Low total serum calcium levels in ICU patients are often attributed to low serum albumin levels. However, low *ionized* calcium concentration occurs in up to 40% of ICU patients. Whereas *chronic* hypocalcemia is often associated with primary abnormalities in PTH and vitamin D levels, *acute*

BOX 39.4 ■ Causes of Hypocalcemia

Hypoparathyroidism (low parathyroid hormone [PTH])
—Primary hypoparathyroidism
—Post-parathyroidectomy ("hungry bone syndrome")
Chelation of calcium
—Acute pancreatitis
—Hyperphosphatemia
—Rhabdomyolysis (early phase)
—Tumor lysis
Drugs
—Bisphosphonates
—Calcitonin
—Foscarnet (via chelation)
—Phenytoin
Hypomagnesemia
Increase albumin binding
—Acute respiratory alkalosis
Vitamin D deficiency

ionized hypocalcemia in ICU patients is more often the result of acute illness, sepsis, pancreatitis, rhabdomyolysis, and hypomagnesemia, although impaired PTH and vitamin D homeostasis are often involved in the underlying pathophysiology. Clinicians must be attentive to the possibility of ionized hypocalcemia even with a low-normal total calcium concentration in patients with alkalemia. Typical causes of acute hypocalcemia are presented in Box 39.4.

Clinical Manifestations

Chronic hypocalcemia may be associated with cutaneous changes (dry skin, brittle nails, coarse hair), dental hypoplasia, cataracts, and calcification of the basal ganglia. Acute hypocalcemia is more typically associated with cardiac and neuromuscular symptomatology. Neuromuscular manifestations are common and potentially life threatening. Mild symptoms include myalgias, muscle cramps and stiffness, acral and circumoral paresthesias, minor twitching, anxiety, fatigue, and depression. More severe manifestations include seizures, laryngeal spasm, papilledema, hallucinations, and psychosis. Trousseau sign (carpopedal spasm induced by inflation of a blood pressure [BP] cuff above systolic BP for 3 minutes) and Chvostek sign (twitching of the facial muscles induced by tapping the ipsilateral facial nerve) may be present in patients with latent tetany. Cardiovascular manifestations of hypocalcemia include hypotension, depressed myocardial function with heart failure, and QT interval prolongation; heart block and other dysrhythmias are less common.

Alkalosis potentiates the effect of hypocalcemia on tetany by reducing ionized calcium levels. Tetany and other symptoms typical of hypocalcemia can also be seen with hypomagnesemia, which is often present in patients with acute hypocalcemia.

Treatment

Treatment of hypocalcemia varies depending on the severity of associated symptoms and concomitant other conditions. Chronic hypocalcemia with few or no symptoms can be treated with oral calcium (1000 to 2000 mg elemental calcium daily) and vitamin D (ergocalciferol, cholecalciferol, calcitriol). In patients with underlying advanced renal failure, use calcitriol or the vitamin D analogues paricalcitol or doxercalciferol, as they do not require renal 1-hydroxylation.

Significant symptoms and other clinical manifestations of hypocalcemia are unusual with corrected total calcium levels > 7.5 mg/dL or ionized calcium levels > 1.2 mmol/L. In patients with symptomatic hypocalcemia, who manifest latent or overt tetany or other features such as QT interval prolongation or hypotension, urgent treatment with intravenous calcium is indicated with 10 to 20 mL of 10% *calcium gluconate* (containing 90 mg elemental calcium in 10 mL and 180 mg in 20 mL) over 20 minutes. *Calcium chloride*, containing 270 mg of elemental calcium per 10 mL, can also be used but is more sclerosing to blood vessels than the gluconate and can cause tissue necrosis if extravasated. This initial infusion can be followed with a continuous infusion delivering 0.5 to 1.5 mg elemental calcium per hour (e.g., 100 mL of 10% *calcium gluconate* in 1000 mL has a concentration of ~1 mg elemental calcium per mL or at a rate of 1 mL/h) with subsequent adjustment based on changes in the serum calcium concentration.

Calcium-containing solutions should not contain or be administered along with other solutions containing bicarbonate or phosphate because of the possibility of precipitation as insoluble salts. They should also not be administered in the same line as blood because of the risk of clotting from reversal of citrate anticoagulation. Frequent monitoring of total or ionized calcium levels and the ECG is critical when calcium is being infused, especially in patients who are taking digitalis, as hypercalcemia can potentiate digitalis toxicity.

Hypomagnesemia is common in patients with hypocalcemia and can itself cause hypocalcemia resulting from the inhibition of PTH secretion and resistance to the effects of PTH. In these patients, correction of hypomagnesemia (discussed later) is necessary for correction of the hypocalcemia. If concomitant acidemia exists, correct hypocalcemia prior to correction of the acidemia, because an increase in blood pH will increase albumin binding of calcium and worsen ionized hypocalcemia. In the setting of severe hyperphosphatemia, as may be seen in patients with advanced renal failure, rhabdomyolysis, and tumor lysis syndrome, intravenous calcium should only be given cautiously—if at all—because of the high risk of tissue deposition of insoluble calcium phosphate. In this setting, hemodialysis may be necessary for phosphate removal and restoration of normal calcium levels.

Magnesium Disorders

The normal magnesium concentration is 1.7 to 2.3 mg/dL (0.71 to 0.96 mmol/L). Thirty percent of the magnesium in the extracellular fluid is protein bound; 60% to 65% is free, ionized magnesium; and 5% to 10% is complexed to citrate, phosphate, oxalate, and other anions. Unlike calcium, magnesium homeostasis and renal handling are not under precise hormonal control, and the plasma magnesium concentration is the most important determinant of renal magnesium excretion. Effects of changes in systemic pH and serum albumin concentration do not predictably alter the serum magnesium concentration.

HYPERMAGNESEMIA

Hypermagnesemia is almost always the result of magnesium ingestion (laxatives, antacids, Epsom salts (magnesium sulfate), use of magnesium-containing enemas, or intravenous administration—most typically for treatment of preeclampsia [Chapter 72]). Sustained hypermagnesemia requires the presence of at least some degree of reduced glomerular filtration rate (GFR), as excess magnesium is normally quickly excreted in the urine.

Clinical Manifestations

Mild hypermagnesemia (serum level < 3.5 mg/dL) is usually asymptomatic. With levels above about 4.5 to 4.8 mg/dL, symptoms are often nonspecific (nausea, headache, drowsiness). With progressively higher serum magnesium levels, more serious symptoms and other

clinical manifestations develop, including loss of deep tendon reflexes, skeletal and respiratory muscle paralysis, paralytic ileus, hypotension, bradycardia, prolongation of the PR interval, an increase in QRS duration, an increase in Q-T interval, heart block, and cardiac arrest. Hypermagnesemia can also induce hypocalcemia because of inhibition of PTH secretion and parasympathetic blockade; the resulting fixed, dilated pupils may be mistaken for brain stem herniation.

Treatment

Treatment of mild symptomatic hypermagnesemia in patients with normal renal function is based simply on cessation of any magnesium administration. In patients with acute or chronic renal failure, hemodialysis can be used to rapidly remove magnesium and reduce the plasma concentration, although this is rarely necessary. Peritoneal dialysis and continuous renal replacement therapies may also be used but are less efficient and will lower the plasma magnesium concentration more slowly than hemodialysis. For emergent treatment, 1000 to 2000 mg of *calcium gluconate* (10 to 20 mL) given intravenously over 5 to 10 minutes will antagonize many of the effects of hypermagnesemia.

HYPOMAGNESEMIA

Hypomagnesemia occurs in as many as two thirds of critically ill patients, often along with other electrolyte disorders, such as hypocalcemia and hypokalemia. The differential diagnosis of hypomagnesemia is broad (Box 39.5), but in general hypomagnesemia is due to renal and gastrointestinal losses, often in combination. In circumstances where the etiology of hypomagnesemia is unclear, a 24-hour urinary magnesium excretion > 1 mmol/24 hours or a calculated fractional excretion of magnesium > 3% suggests inappropriate renal wasting (see Box 39.E1 for a formula that can be used to calculate FE_{Mg}). The FE_{Mg} can decrease to < 0.5% with magnesium depletion from nonrenal causes.

Clinical Manifestations

Hypomagnesemia is usually asymptomatic when plasma levels are above about 1.2 mg/dL, although the relationship between total body magnesium and plasma levels is not precise. More severe hypomagnesemia can be associated with manifestations similar to those described previously with

BOX 39.5 ■ Causes of Hypomagnesemia

Chelation of Magnesium

Pancreatitis

Gastrointestinal (GI) Losses

Diarrhea
Malnutrition (resulting from constitutive GI loss)

Renal Losses

Alcohol intoxication
Diuretics (loop or thiazide)
Hypercalcemia
Postacute tubular necrosis (ATN) diuresis
Postobstructive diuresis

Tissue Reuptake

"Hungry bone" syndrome

BOX 39.E1 ■ Formula to Calculate Fractional Excretion of Magnesium (FE[Mg]) > 3% Suggests Renal Magnesium Wasting)

$$FE(Mg) = \{UMg/0.7 \times PMg\}/\{Ucr/Pcr\} \times 100$$

Where:
FE(Mg) = fractional excretion of magnesium (%)
UMg = urinary concentration of magnesium (mmol/L)
PMg = plasma concentration of magnesium (mmol/L)
Ucr = urinary concentration of creatinine (g/dL)
Pcr = plasma concentration of creatinine (g/dL)

Note: The plasma magnesium concentration, P_{Mg}, is multiplied by 0.7 because about 70% of total plasma magnesium is not albumin bound and is thus free to be filtered across the glomerulus.

hypocalcemia, including muscle excitability (tremors, twitching, seizures, tetany) as well as muscle weakness and paralysis (including respiratory muscles). ECG changes include QRS complex widening, increased QT interval, and peaked T waves; more severe hypomagnesemia leads to prolongation of the PR interval, further widening of the QRS complex, development of prominent U waves, and diminution or inversion of T waves. Both supraventricular and ventricular cardiac tachyarrhythmias are common, including *torsades de pointes* and ventricular fibrillation in the setting of severe hypomagnesemia. Hypomagnesemia also increases the risk of digitalis cardiac toxicity.

Magnesium depletion induces urinary potassium wasting, so hypomagnesemia is commonly associated with hypokalemia that remains refractory to treatment until the magnesium deficiency is corrected. Hypocalcemia is also common in patients with hypomagnesemia because of resistance to the skeletal effects of PTH and reduced PTH secretion. This hypocalcemia will also be refractory to treatment until the magnesium deficiency is corrected.

Treatment

Patients with asymptomatic hypomagnesemia should receive oral replacement therapy. An initial oral dose of 30 to 60 mEq per day in three or four divided doses can be used, preferably with a sustained release preparation (*magnesium chloride* 5.3 mEq/tablet or magnesium lactate 7 mEq/tablet). *Magnesium oxide* (400 mg tablet with 20 mEq of elemental magnesium) two to three times daily may also be adequate, but diarrhea occurs more commonly with this than with sustained released formulations. Repletion of depleted body stores usually takes at least several days. Amiloride and the other K^+-sparing diuretics can reduce the renal magnesium wasting that occurs with the use of other diuretics, aminoglycosides, and amphotericin B, and in patients with Gitelman's syndrome or other magnesium-wasting conditions.

Patients with symptomatic or more severe hypomagnesemia should receive IV *magnesium sulfate* ($MgSO_4$). Because the serum magnesium concentration is the primary determinant of urinary excretion, approximately half of an intravenous dose of magnesium is quickly lost in the urine, even in the presence of ongoing magnesium deficiency. Therefore, sustained-release oral preparations or slow intravenous infusions are recommended after initial correction to maintain serum magnesium concentration.

An IV dose of magnesium of 1 to 1.5 mEq/kg can be given over the first 24 hours, with doses of 0.5 to 1 mEq/kg daily thereafter until the plasma magnesium level remains within the normal range. One gram of $MgSO_4$ (as $MgSO_47H_20$) contains 8.1 mEq (98.7 mg) of elemental magnesium; 8 to 12 grams can be given intravenously over the first 24 hours with an additional 4 to 6 grams per day for several additional days as needed. Lower doses should be given in patients with reduced kidney function. In emergency situations, 1 to 2 grams of $MgSO_4$ (8.1 to 16.2 mEq) can be given intravenously in 50 mL of normal saline or 5% dextrose in water over 5 to 10 minutes. Magnesium sulfate can be painful and sclerosing when administered intravenously, so it should be diluted prior to administration. Patients should be monitored during magnesium infusion for hypotension and reduction of deep tendon reflexes.

Phosphate Disorders

Like calcium, phosphorous is under hormonal regulation by vitamin D, which increases GI tract absorption and PTH, which increases renal phosphorous excretion. Fibroblast growth factor-23 (FGF-23) and other phosphatonins also potently inhibit renal phosphate reabsorption. The plasma phosphate concentration also directly regulates its own reabsorption in the kidney; hypophosphatemia leads to increased phosphorus absorption and reduced excretion. Most of the body's phosphorus is present in bone (> 80%) and in the form of intracellular organic phosphate compounds. The plasma phosphate concentration (normally 2.5 to 4.5 mg/dL) is

BOX 39.6 ■ Causes of Hypophosphatemia

Chronic alcoholism
Decreased intestinal absorption
—Antacids
—Chronic diarrhea/malabsorption
Malignancy
—Parathyroid hormone-related protein (PTH-RP) releasing tumors
—Oncogenic osteomalacia
Renal phosphate wasting
—Drugs (ifosfamide, cyclophosphamide, cisplatin, aminoglycosides)
—Loop diuretics
—Primary hyperparathyroidism
—Recovery phase of diabetic ketoacidosis
Shift into bone
—Burns (cytokine mediated)
—Hungry bone syndrome
—Refeeding syndrome (Chapter 15)
—Respiratory alkalosis

measured in the clinical chemistry laboratory as the concentration of phosphorus in inorganic phosphates, which are mostly in the form of free HPO_4^{-2} and $H_2PO_4^{-}$ ions in a molar ratio of 4:1 at normal blood pH. Because the valence of inorganic phosphate ion changes with changes in pH, the phosphate concentration is preferably expressed in mmol/L or mg/dL (1 mmol/L = 31 mg/dL).

HYPOPHOSPHATEMIA

Mild hypophosphatemia is seen frequently in ICU patients; common causes of hypophosphatemia are listed in Box 39.6. In general, intracellular shift of phosphate, renal phosphate wasting, GI losses, and poor intake of phosphate are the overriding pathophysiologic processes; many patients have multiple contributing factors. Inappropriate urinary phosphate wasting is suggested by a urine phosphate > 100 mg/dL or fractional excretion of phosphate > 5%. Hypophosphatemia can be present with low, normal, or high total body phosphate, as a function of what can be substantial shifts of phosphate from the extracellular to intracellular compartments. Likewise, phosphate depletion can be present with normal or even elevated plasma levels. Patients with chronic alcoholism, diabetic ketoacidosis (DKA), acute respiratory alkalosis, and the "refeeding syndrome" are particularly prone to develop severe acute hypophosphatemia. In chronic alcoholics, even with initially normal serum phosphate levels, there is often profound total body phosphate depletion, and potentially severe hypophosphatemia should be anticipated.

Clinical Manifestations

Symptoms and signs of hypophosphatemia are for the most part related to the depletion of intracellular adenosine triphosphate (ATP) with disruption of many critical cellular functions, and to decreases in erythrocyte 2,3-diphosphoglycerate (2,3-DPG). Low levels of 2,3-DPG cause increased hemoglobin affinity for oxygen, thereby decreasing oxygen delivery to peripheral tissues. Most patients with clinically significant manifestations of hypophosphatemia will have serum levels below 1.5 to 2 mg/dL.

Chronic hypophosphatemia is associated with bone resorption, decreased bone mineralization, hypercalciuria, rickets, and osteomalacia. More pertinent sequelae in the ICU patient with acute hypophosphatemia include rhabdomyolysis (which is especially likely in the alcoholic patient with hypophosphatemia), depression of myocardial and respiratory muscle function with (usually but not always) reversible cardiac output impairment and respiratory failure, skeletal muscle weakness and impairment of GI tract motility, and irritability, paresthesias, confusion, seizures, and coma thought to be due to central nervous system (CNS) ischemia. Although hypophosphatemia also impairs red cell, leukocyte, and platelet function, clinically significant hemolysis and platelet dysfunction are rare. Finally, it is unproven that acute hypophosphatemia itself increases the risk for infection or sepsis.

Treatment

Treatment of hypophosphatemia is indicated if it is severe (less than 1 mg/dL), if the patient is symptomatic, or if the clinical history suggests total body phosphorus depletion (e.g., chronic alcoholism). Acute hypophosphatemia resulting from the transcellular relocation of phosphorus with normal total body phosphorus requires treatment of the underlying process (i.e., acute respiratory alkalosis) and not phosphorus supplementation. On the other hand, cellular uptake of phosphorus with the refeeding syndrome and in chronic alcoholics is associated with total body phosphorus depletion and requires exogenous phosphorus supplementation. Patients with hypophosphatemia associated with DKA most often correct spontaneously with resumption of normal dietary intake and do not therefore usually require phosphorus supplementation. Patients with hypophosphatemia caused by vitamin D deficiency or impaired vitamin D homeostasis should receive appropriate vitamin D replacement.

Repletion of phosphorus is empiric because serum phosphate levels do not accurately predict phosphorus stores. Any oral phosphate binders should be discontinued. Oral or enteral replacement therapy is preferred, if possible. The easiest and safest vehicle is milk, which contains approximately 0.9 to 1 mg of phosphorus per mL. Alternatively, a reasonable regimen for a typical patient would be 1000 to 2000 mg (32 to 64 mmol) of elemental phosphate daily for 7 to 10 days; higher doses can be given if appropriate and may be required particularly in patients with ongoing renal phosphate wasting. Because oral or enteral phosphate supplements often cause diarrhea, higher doses may not be well tolerated. Oral phosphate supplements contain varying amounts of sodium or potassium (Box 39.7), a factor that should be considered in patients with hypo- or hyperkalemia or in whom sodium restriction is important.

If oral or enteral access is not possible, initiate parenteral therapy with 1000 to 3000 mg (30 to 90 mmol) elemental phosphate per day and frequently monitor serum phosphate and calcium concentrations. A recommended approach is to provide 0.08 to 0.16 mmol (2.5 to 5 mg) per kg of elemental phosphorus over 6 hours depending on the estimated severities of the phosphorus deficit and associated complications. Note that hypophosphatemia-induced rhabdomyolysis might be complicated by hyperphosphatemia (and often hypocalcemia) from phosphorus released by injured skeletal muscle. Complications of parenteral phosphate therapy (Box 39.7) include hypocalcemia, hyperkalemia or hypernatremia (depending on whether provided as a potassium- or sodium-containing preparation), and metastatic calcification.

HYPERPHOSPHATEMIA

The ability of the normally functioning kidneys to excrete large phosphorus loads is quite robust, so most patients with hyperphosphatemia have some degree of reduced GFR, because of either acute kidney injury or chronic kidney disease, typically with a GFR < 25 to 30 mL/min. Causes of hyperphosphatemia are shown in Box 39.8. Large acute exogenous phosphorus loads or massive release of intracellular phosphorus into the extracellular fluid can cause hyperphosphatemia in the

BOX 39.7 ■ Oral and Intravenous Phosphorous Replacement

Severe hypophosphatemia (< 1.0 mg/dL): IV replacement with 0.08–0.24 mmol/kg over 4–6 hours
Moderate hypophosphatemia (1.0–2.0 mg/dL): IV replacement as above if symptomatic; otherwise oral replacement with 1–1.5 mmol/kg (up to 100 mmol) per day in 3–4 divided doses
Mild hypophosphatemia (> 2.0 mg/dL): Oral therapy with 1 mmol/kg (up to 80 mmol) per day in 3–4 divided doses
IV replacement: sodium phosphate (each mL contains 93 mg phosphate and 4 mEq sodium) or potassium phosphate (each mL contains 93 mg phosphate and 4 mEq potassium)
Oral therapy (quantity providing 1000 mg phosphate [32 mmol])
- Skim milk: 1L
- Neutra-Phos: 4 capsules (28 mEq sodium and 28 mEq potassium)
- Neutra-Phos-K: 4 capsules (56 mEq potassium)
- K-Phos: 9 tablets (33 mEq potassium)
- K-Phos-Neutral: 4 tablets (48 mEq sodium and 8 mEq potassium)

BOX 39.8 ■ Causes of Hyperphosphatemia

Decreased Renal Excretion

Acute or chronic kidney disease
Bisphosphonates
Hypoparathyroidism
Thyrotoxicosis
Cinacalcet (in patients not on dialysis)

Exogenous Phosphate Load

Gastrointestinal (GI) preparations containing phosphate
Intravenous phosphate

Shift from Intracellular Fluid (ICF) to Extracellular Fluid (ECF)

Hemolysis (if severe)
Malignant hyperthermia
Metabolic acidosis
Rhabdomyolysis
Tumor lysis syndrome

absence of severely impaired kidney function (but may lead to acute kidney injury). Exogenous phosphorus loads are most commonly due to administration of phosphate salts used as a laxative, purgative for colonoscopy, or enema. One commonly used preparation, oral sodium phosphate, contains 21 mmol/5 mL of elemental phosphorus. This and similar preparations have been associated with severe hyperphosphatemia, hypocalcemia, acute kidney injury, CKD, nephrocalcinosis, and death. Internal redistribution of phosphorus is most commonly the result of acute respiratory acidosis, rhabdomyolysis, and tumor lysis syndrome; the latter two disorders can also be associated with other electrolyte abnormalities (hyperkalemia, metabolic acidosis, hypocalcemia) and hyperuricemia.

Clinical Manifestations

Symptoms of hyperphosphatemia are primarily related to contemporaneous hypocalcemia (tetany, paresthesias, etc.) and to the metastatic calcification of soft tissues, including the cardiac conducting system. The hypocalcemia associated with hyperphosphatemia is due to

inhibition or 1,25-$(OH)_2$ vitamin D, precipitation of calcium-phosphate salts, and impairment of GI tract calcium absorption.

Treatment

Chronic or acute hyperphosphatemia that is not associated with symptomatic hypocalcemia is managed primarily by a low-phosphorus diet (800 to 1000 mg/d) and the use of oral phosphate binders. Oral phosphate binders (see Table 39.E1) are most effective when given with meals, although there may be a small effect even in patients who are not eating or receiving enteral nutrition. Aluminum-containing phosphate binders are potent but associated with bone, muscle, CNS, and other toxicities and are now used primarily for only short-term treatment of severe hyperphosphatemia. Aluminum hydroxide must be avoided in patients receiving oral citrate-containing preparations because citrate increases GI tract absorption of aluminum and predisposes to acute aluminum toxicity. Exogenous sources of phosphorus (such as parenteral nutrition) should be eliminated if possible. In the absence of renal failure, administration of 1 to 2 L of isotonic saline over 2 hours will increase urinary phosphate excretion. Hemodialysis has a role in the management of hyperphosphatemia in patients with acute kidney injury and CKD, but it is relatively inefficient for removing phosphorus.

An annotated bibliography can be found at www.expertconsult.com.

TABLE 39.E1 ■ **Oral Phosphate Binders**

Generic Name	Brand Name	Dosage (Usual Starting Dose; Given Three Times Daily with Meals)	Cautions and Notes
Aluminum hydroxide	Amphojel* AlternaGEL,* Alu-Tab others	500–600 mg	Limits use to short-term administration for severe hyperphosphatemia because of the risk of aluminum toxicity; avoid with concomitant citrate-containing preparations
Calcium carbonate	TUMS, OsCal, others	500–1000 mg	Avoid with hypercalcemia; inexpensive
Calcium acetate	Phoslo	667–1334 mg	Avoid with hypercalcemia
Lanthanum carbonate	Fosrenol	500–750 mg	Limited long-term data, higher cost, does not contain calcium or aluminum
Sevelamer HCl	Renagel	800–1600 mg	Higher cost with similar efficacy to calcium-based binders; some patients develop metabolic acidosis; does not contain calcium or aluminum
Sevelamer carbonate	Renvela	800–1600 mg	Higher cost, less risk of metabolic acidosis, does not contain calcium or aluminum

*600 mg/5 mL suspension.

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CHAPTER 40

Ileus

Paul Menard-Katcher ■ Gary R. Lichtenstein

Ileus, an inhibition of gastrointestinal motility, commonly occurs in patients in the intensive care unit (ICU). Ileus can be a physiologic response—for example, after abdominal surgery—or it may be pathologic. The presence of ileus may be associated with significant morbidity because it restricts patients from normal use of their gastrointestinal tract. Because of its high prevalence and potentially adverse effects, the recognition and management of ileus are important in the care of patients in the ICU.

Ileus (also called adynamic ileus) is defined as the functional inhibition of propulsive bowel activity, irrespective of pathogenic mechanism. This differs from other gastrointestinal motility disorders resulting from structural abnormalities—for example, small bowel obstruction. *Postoperative ileus* is the uncomplicated ileus that follows surgery and usually resolves spontaneously within 2 to 3 days. Prolonged postoperative ileus lasts longer than 3 days. Ileus of the colon with sudden massive dilatation is called *acute colonic pseudo-obstruction* or *Ogilvie syndrome*. *Toxic megacolon* is another form of colonic ileus in which inflammation involves all colonic tissue layers and that results in systemic toxicity.

Pathophysiology

A multitude of pathologic phenomena are associated with the presence of an ileus. Inflammation (either postoperative or systemic) predisposes to ileus. An *impairment of intestinal blood flow* (arterial or venous) can lead to an ileus. Conversely, the presence of a simple ileus itself does not lead to the impairment of intestinal blood flow. Analogous to that which occurs in states of mechanical bowel obstruction, a *change in bowel flora* may also occur during ileus. This can lead to stasis, overgrowth of bacteria, and subsequent malabsorption. There may also be a *change in the bowel contents* similar to that which occurs in distended loops of bowel during intestinal obstruction. Under these circumstances, fluid inside the bowel lumen increases because of intestinal secretion plus a failure of absorption. Intestinal gas also contributes to the abdominal distention, and the gas-filled loops of intestine are routinely seen on the abdominal radiograph of a patient with ileus. In the case of ileus, this gas results primarily from swallowed air.

Significant *changes in motility* occur in both the small and large intestine in the presence of ileus. Unfortunately, the mediators of these changes have not yet been identified, even in postoperative ileus (although several neurohormonal peptides have been studied as potential candidates). Although it has been suggested that adrenergic mediation is responsible, this does not explain why the ileus persists for several days. Also, evidence suggests that mechanisms other than spinal reflexes play a role because the use of nonopioid epidural anesthesia (which blocks efferent sympathetic nerves) does not shorten the duration of ileus. Although damage to cholinergic nerves from hypoxemia or from surgical manipulation could explain some cases of ileus, activation of the nonadrenergic, noncholinergic inhibitory nerves is the most likely cause for most cases of ileus.

Causes of Ileus in the Intensive Care Unit

Common intra-abdominal and extra-abdominal causes of ileus that would be relevant for patients in the ICU are listed in Boxes 40.1 and 40.2. Likewise, intra-abdominal and

BOX 40.1 ■ Intra-abdominal Causes of Ileus

Infectious Disorders

- Peritonitis
- Diverticulitis
- Cholecystitis
- Appendicitis
- Tubo-ovarian abscess

Inflammatory Disorders

- Pancreatitis
- Perforated viscus
- Toxic megacolon
- Intraperitoneal bleeding
- Peritonitis
- Radiation

Ischemic Disorders

- Local arterial insufficiency
- Local venous insufficiency
- Mesenteric arteritis
- Strangulated obstruction

Retroperitoneal Disorders

- Nephrolithiasis
- Pyelonephritis
- Hemorrhage

BOX 40.2 ■ Extra-abdominal Causes of Ileus

Drug Induced

- Anticholinergic medication
- Opioids
- Chemotherapy
- Ganglionic blocking agents

Metabolic Disturbances

- Electrolyte abnormalities
- Sepsis
- Uremia
- Diabetic ketoacidosis
- Sickle cell anemia with painful crisis
- Hypothyroidism

Reflex Inhibition

- Myocardial infarction
- Pneumonia
- Pulmonary embolus
- Burns
- Fractures of the pelvis, ribs, or spine

BOX 40.3 ■ Intra-abdominal Disorders Associated with Acute Colonic Pseudo-obstruction

Inflammatory Disorders
- Acute pancreatitis
- Acute cholecystitis
- Inflammatory bowel disease
- Radiation colitis

Infectious Disorders
- Herpes simplex or herpes zoster infection
- Spontaneous bacterial peritonitis

Ischemic Disorders
- Inferior mesenteric artery insufficiency

Retroperitoneal Disorders
- Neoplasms
- Bleeding

Reflex Inhibition
- Trauma
- Cholecystectomy
- Urologic operations
- Cesarean section

BOX 40.4 ■ Extra-abdominal Disorders Associated with Acute Colonic Pseudo-obstruction

Medication Related
- Phenothiazines
- Chemotherapy
- Laxative abuse
- Tricyclic antidepressants

Metabolic Disorders
- Systemic infection
- Chronic obstructive pulmonary disease with acute exacerbation
- Ethanol

Reflex Inhibition
- Bone fractures
- Coronary artery bypass graft surgery
- Valvular heart surgery

extra-abdominal conditions associated with acute colonic pseudo-obstruction or Ogilvie syndrome (a nonobstructive, acute massive dilatation of the colon that is temporary and reversible) are listed in Boxes 40.3 and 40.4.

Diagnostic Evaluation of the ICU Patient with Ileus

Initial steps include evaluation for electrolyte disturbances (measuring serum sodium, potassium, chloride, and bicarbonate levels) and searching for evidence of infection or inflammatory

disorders (e.g., obtaining a white blood cell count with differential). In ischemic or infarcted bowel, the presence of other laboratory abnormalities may be found, including elevated levels of serum amylase, alkaline phosphatase (ALP), creatinine phosphokinase (CPK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) as well as an anion gap metabolic acidosis. However, all of these laboratory abnormalities are nonspecific.

In patients with suspected ileus, it is important to obtain an obstruction series—that is, abdominal radiographs (supine and upright views)—to help localize the abnormality and to exclude free intraperitoneal air. Chest radiographs can indicate the presence of associated pulmonary disease as an extra-abdominal cause of the ileus. When an ileus is present, intestinal gas and fluid are present in various amounts throughout the intestinal tract. In contrast, in acute colonic pseudo-obstruction, only the large bowel becomes dilated throughout its extent. However, it is typically the cecum that is greatest in diameter. Computed tomography (CT) can be helpful in assessing the presence of thickened bowel loops (suggestive of ischemia), abscesses, pancreatic disease, venous thrombosis, and other similar disorders. CT should be considered only if plain radiographs are inconclusive.

Differentiating ileus from mechanical obstruction may be difficult and require a barium enema, colonoscopy, or small bowel contrast radiography. However, care should be taken to avoid administration of barium proximal to an area of obstruction because it can become trapped, inspissated, and impacted. Magnetic resonance (MR) imaging (with MR venography or MR angiography) has been used with increasing frequency in selected patients. In these cases, plain abdominal radiographs are not revealing, and either pancreatic disease or venous disease (such as mesenteric venous thrombosis) is suspected or CT is not performed because of contrast allergy or renal insufficiency.

Endoscopy, colonoscopy, or enteroscopy may be of value if the bowel mucosa must be visualized or biopsied. However, these procedures should be avoided if a perforated viscus or an acute abdomen is present. When an ileus is associated with ascites without a clear cause, a paracentesis should be performed to search for several abnormalities, including signs of infection (elevated white blood cells, positive culture), high amylase levels, and the presence of malignant cells.

Management and Discussion of Therapies

In the postoperative period, an ileus is expected and typically resolves within a few days. The initial management should entail ruling out the presence of bowel obstruction and whether there are associated fluid, electrolyte, or acid base disorders. Electrolytes should be repleted as needed. Patients should receive nothing by mouth. Although the routine placement of a nasogastric tube is not required, if the bowel is distended, initiation of nasogastric suction with low intermittent suctioning is appropriate because bowel distention can result in nausea, vomiting, and an increased risk of aspiration. One should avoid, if possible, the use of opioids and other agents (see Box 40.2) that may slow down bowel motility.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used as alternatives to opioids for pain management. Peripherally acting mu-opioid receptor antagonists are under investigation for the treatment of postoperative ileus, but thus far they have yet to show proven benefit in clinical trials. One agent in particular, alvimopan, may reduce the times to gastrointestinal recovery and hospital discharge after abdominal surgery. Interestingly, chewing gum may reduce the duration of post-operative paralytic ileus following surgery.

Acute bowel obstruction is a surgical emergency. Surgery is also necessary in some patients with ischemic small bowel disease. In contrast, ischemic colonic disease has a low mortality. Thus, surgery should be contemplated only when symptoms persist or if the bowel is suspected of being infarcted. The therapy for ileus should be directed primarily toward the treatment of its underlying cause.

In patients with acute colonic pseudo-obstruction, appropriate management of fluid and electrolytes is of key importance. Patients are usually kept fasting and treated with intravenous (IV) fluids and a nasogastric (NG) tube with low intermittent suction. When resolution is slow with the use of an NG tube alone, a rectal tube should be placed to low intermittent suction. Opioids and other antimotility agents should be withdrawn, and efforts to correct any underlying associated condition should be made. If conservative care fails, giving 2 mg IV neostigmine has been reported as being highly effective. If the colonic diameter becomes large (usually > 12 cm in maximal transverse dimension), ischemia, perforation, and sepsis may ensue. Even in the case of a massively dilated colon, conservative management via NG tube, rectal tube, avoidance of antimotility agents, and neostigmine should be attempted initially. This approach is usually successful, but more aggressive decompression may be needed either by colonoscopy or by surgical cecostomy.

Clinical Pearls and Pitfalls

Several key points can be summarized in the following general guidelines:

1. Look at medications and discontinue antimotility agents (see Box 40.2).
2. Check obstruction series and chest radiograph.
3. Check electrolytes and complete blood count with differential and thyroid status.
4. Consider colonoscopic or endoscopic procedures.
5. Look for complications of systemic diseases.
6. Look for evidence of ischemic bowel disease.
7. Consider CT examination to search for a cause of ileus.
8. In acute colonic pseudo-obstruction, follow obstruction series and attempt decompression via nasogastric tube, rectal tube, and, if needed, colonoscopy or surgical cecostomy while attempting to reverse the associated cause (see Boxes 40.3 and 40.4).

Summary

It is common for a patient to acquire an ileus during a stay in the ICU. The presence of an ileus can lead to significant morbidity and possibly mortality. A rapid and efficient search for the cause of the ileus is critical to reduce this morbidity and to restore enteral nutrition promptly.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 41

Increased Intracranial Pressure

Joshua M. Levine ■ David N. Levine ■ Diana Goodman

An acute rise in intracranial pressure (ICP) in patients in the intensive care unit (ICU) is a life-threatening cranial compartment syndrome that requires emergent treatment. In adults, the cranial contents are bounded by a rigid skull, which is noncompliant and unable to accommodate additional volume. Intracranial hypertension becomes deleterious when it reduces cerebral blood flow or when it results in mechanical compression of brain tissue. Clinically, intracranial hypertension is often inferred from neurologic examination, from changes in vital signs, or from findings on neuroimaging studies. ICP may be measured directly during lumbar puncture or with a variety of ICP monitors. Standardized indications for ICP monitoring have been established by the Brain Trauma Foundation for patients with traumatic brain injury (Chapter 99), but they are lacking in other disease states. Initial therapy for acute intracranial hypertension is often empiric, but its cause should be sought immediately.

This chapter discusses fundamental physiologic concepts, the pathophysiology of intracranial hypertension, differential diagnoses and herniation syndromes, and an approach to diagnosis and treatment.

Physiology

The goal of resuscitation in the neurocritical care patient is to provide sufficient delivery of fuel, typically oxygen and glucose, to meet cerebral cellular metabolic demand. Fuel delivery is largely determined by cerebral blood flow (CBF), which is difficult to measure directly at the bedside. Cerebral perfusion pressure (CPP) is therefore commonly used as a surrogate for CBF. CPP is calculated as the difference between mean arterial pressure (MAP) and ICP. The relationship between CBF and CPP may be approximated using Poiseuille's law, which describes flow through a rigid tube. Modeled this way, CBF is directly proportional to CPP and to the vessel radius raised to the fourth power, and it is inversely proportional to blood viscosity. Under normal circumstances, cerebral autoregulation maintains constant CBF across a wide range of CPP through modulation of vascular diameter. In many disease states (e.g., traumatic brain injury), however, vasoplegia and impaired autoregulation develop, disrupting this relationship (Figure 41.1). When this occurs, CBF becomes linearly related to CPP (CBF becomes "pressure passive"), and it becomes crucial to closely monitor and tightly control CPP. This necessitates measurement and control of ICP.

The Monro-Kellie doctrine defines intracranial pressure (ICP) as the sum of the pressures exerted by the intracranial contents, namely brain tissue, blood, and cerebrospinal fluid (CSF). It is intuitive that each of these components exerts pressure because of its volume. However, the relationship between intracranial volume and intracranial pressure is nonlinear. The intracranial compliance (change in volume per unit change in pressure) curve is logarithmic (Figure 41.2). The intracranial compartment may absorb from 100 to 150 mL of additional volume without a significant change in ICP because of a variety of compensatory mechanisms such as collapse of the low-pressure veins and egress of CSF into the lumbar subarachnoid space. Once these

compensatory mechanisms are exhausted, however, additional volume results in a rapid rise in ICP. Normal ICP is roughly 6 to 12 mm Hg, and, by convention, intracranial hypertension is defined as ICP > 20 mm Hg.

The average volume of CSF in the adult is ~140 mL, of which ~20% is in the ventricular system, 60% is in the intracranial subarachnoid space, and 20% is in the spinal subarachnoid space. CSF is an ultrafiltrate of plasma and is largely produced by the choroid plexus, focal invaginations

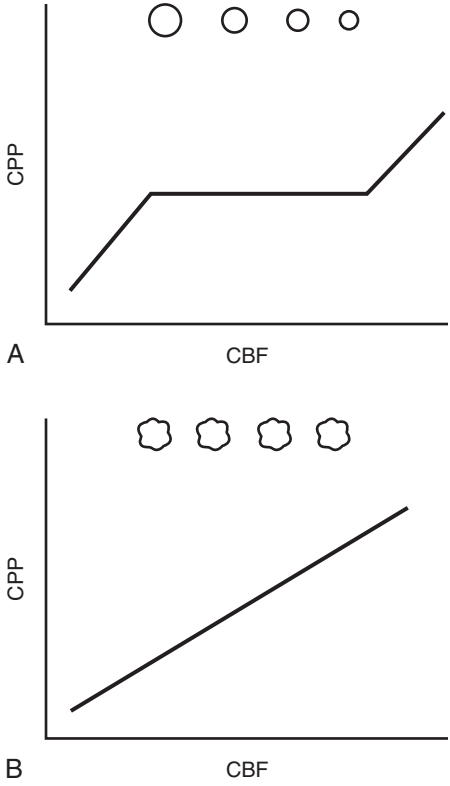


Figure 41.1 Schematic of autoregulation of cerebral blood flow (CBF) and its absence. A, Normal cerebral autoregulation maintains CBF constant over a wide range of cerebral perfusion pressure (CPP) because of modulation of vascular diameter (illustrated by decreasing size of circles with increasing CBF). B, Absent autoregulation in which CBF is linearly related to CPP due to vasoplegia (illustrated by irregular symbols of the same size despite increasing CBF).

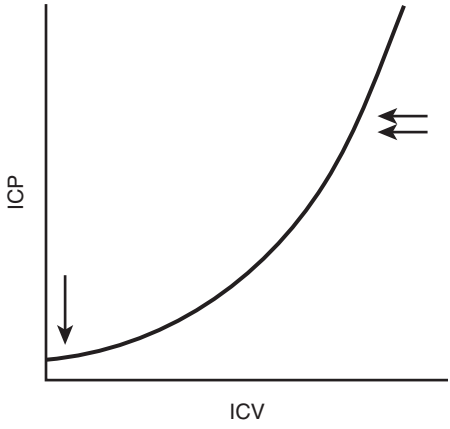


Figure 41.2 Schematic diagram illustrating effects of intracranial compliance. The relationship between intracranial volume (ICV) and intracranial pressure (ICP) is logarithmic. The brain can normally accommodate an additional 100 to 150 mL of volume without a substantial change in pressure because its compliance (change in ICV/change in ICP or ΔICV/ΔICP) is normally high (single arrow, flat portion of curve). However, when ICP is elevated, compliance is low (double arrows, steep portion of curve) so that even small changes in volume result in large changes in pressure. Typically, when ICP is normal, compliance is high; conversely, when ICP is high, compliance is low.

of the pia and its vessels into the lumen of the ventricles. CSF production is normally balanced by CSF reabsorption. When CSF exits the ventricles, it flows into the subarachnoid space and is absorbed into venous blood via arachnoid villi, small projections of arachnoid within the cerebral dural sinuses.

Pathophysiology and Differential Diagnosis

The causes of intracranial hypertension may be divided mechanistically into disorders of CSF dynamics, hydrocephalus, cerebral edema, and mass lesions. Box 41.1 provides a limited differential diagnosis for intracranial hypertension, categorized by cause.

BOX 41.1 ■ Differential Diagnosis of Intracranial Hypertension

Disordered CSF Dynamics

- CSF overproduction
  - Extremely rare cause; may be seen with choroid plexus papilloma
- Impaired CSF absorption
  - Pseudotumor cerebri
    - —Idiopathic
    - —Hypervitaminosis A, isotretinoin use
    - —Increased CSF protein content
  - Ventriculoperitoneal shunt malfunction
- Increased dural sinus pressure
  - Cerebral venous sinus thrombosis
  - Venous sinus compression (e.g., tumor, hemorrhage)
  - Incorporation of venous sinus into AVM

Hydrocephalus

- Noncommunicating
  - Intraventricular hemorrhage, tumor
  - Extrinsic compression of ventricle by hemorrhage, tumor, edema
- Communicating
  - Subarachnoid hemorrhage
  - Carcinomatous or lymphomatous meningitis
  - Infectious meningitis

Cerebral Edema

- Osmotic
  - Acute hyponatremia
  - Rapid hemodialysis
- Vasogenic
  - Hypertensive encephalopathy
  - Tumor-related edema
- Cytotoxic
  - Acute ischemic stroke
  - Fulminant hepatic failure

Mass Lesions

- Tumor—primary or metastatic
- Abscess
- Hematoma (intraparenchymal, subarachnoid, subdural, epidural)

CSF, cerebrospinal fluid; AVM, arteriovenous malformation.

DISORDERS OF CSF DYNAMICS

Disorders of CSF dynamics—overproduction, high resistance to absorption, or high dural sinus pressure—may cause intracranial hypertension. Each of these conditions presents with the syndrome of benign intracranial hypertension, which is characterized by headache, visual obscurations, papilledema, and small (slitlike) ventricles on CT or MRI scans. If left untreated, visual loss may result from permanent injury to the optic nerves. In clinical practice, intracranial hypertension from CSF overproduction is not observed: however, elevated ICP from increased resistance and elevated dural sinus pressure is relatively common.

Pseudotumor cerebri results from increased resistance to CSF absorption at the arachnoid villi. Most cases are idiopathic and usually occur in obese young women. However, known causes include hypervitaminosis A and the use of isotretinoin, a vitamin A derivative. Occasionally, very high CSF protein content, as might be seen in patients with the Guillain-Barré syndrome, systemic lupus erythematosus, or spinal cord tumors, may also cause pseudotumor cerebri, presumably by blocking CSF outflow from the arachnoid villi. Treatment includes weight loss, carbonic anhydrase inhibitors (to decrease CSF production), and, in severe cases, where visual loss is progressive, surgery (CSF diversion or optic nerve sheath fenestration).

Increased dural venous sinus pressure may cause intracranial hypertension and can result from superior sagittal sinus thrombosis, compression from a mass or surgery, or occasionally may be due to an arteriovenous fistula or malformation. Cerebral venous sinus thrombosis is the most commonly encountered cause and may occur spontaneously or as a result of hypercoagulable states, dehydration, trauma, or infection (mastoiditis, meningitis). There is an increased incidence in women who are in the third trimester of pregnancy or in the immediate postpartum state. Venous sinus thrombosis typically presents with headache. In severe cases, venous infarction or hemorrhage occurs and focal neurologic deficits may be observed. Treatment includes systemic anticoagulation to limit clot propagation and, for refractory cases, endovascular thrombolysis. Antibiotics are also used in cases related to infection.

HYDROCEPHALUS

Hydrocephalus refers to progressive dilation of the ventricles caused by obstruction of CSF circulation. In *noncommunicating* hydrocephalus, the obstruction lies within the ventricular system, and ventricular expansion occurs proximal to the obstruction. In *communicating* hydrocephalus, obstruction in the intracranial subarachnoid space causes the ventricles to dilate uniformly. Hydrocephalus may be accompanied by either normal or elevated ICP, and the reason for this variability is incompletely understood. In general, intracranial hypertension is more likely to accompany acute, rather than slowly developing, hydrocephalus.

Hydrocephalus has protean causes. Acute high-pressure hydrocephalus may be communicating or noncommunicating and is a medical emergency. The ventricular system may be acutely compressed or obstructed by tumor, blood, or cerebral edema. Alternatively, the arachnoid villi may be obstructed, for example, by blood (subarachnoid hemorrhage), by inflammation (meningitis), or by tumor cells. Treatment of hydrocephalus is CSF diversion, typically with an external ventricular drain in the acute period, and later, if necessary, an internal drain (e.g., ventriculoperitoneal shunt).

CEREBRAL EDEMA

Normally, the brain capillary endothelium contains tight junctions (blood-brain barrier) that restrict the movement of crystalloids and proteins. Furthermore, brain cells (neurons, astrocytes) rely on pumps to maintain ionic gradients between the intracellular and extracellular spaces.

Cerebral edema, or increased brain water content, has three major causes: (1) a hypo-osmolar state (osmotic edema), (2) altered brain capillary permeability (vasogenic edema), and (3) failure of cell membrane ion pumps or accumulation of osmotically active particles within brain cells (cytotoxic edema). Brain edema may be diffuse or localized, and, if severe, it may cause intracranial hypertension.

When the brain is exposed to hypo-osmolar (hypotonic) plasma, water enters the brain with swelling of the extracellular and intracellular spaces. Clinically this may occur with acute hyponatremia (e.g., from syndrome of inappropriate antidiuretic hormone [SIADH] or water intoxication [Chapter 84]), or with rapid hemodialysis, and affects the brain diffusely. Symptoms include headache, confusion, and seizures, and, if severe, stupor and coma. The goal of treatment is to restore plasma osmolarity (Chapter 84).

Vasogenic edema is caused by altered capillary permeability causing leakage of crystalloids, with or without leakage of proteins, and culminates in expansion of the interstitial (extracellular) space. It may occur from injury to previously healthy vascular endothelium, such as with hypertensive encephalopathy, or it may be due to leakage from new or abnormal blood vessels, such as occurs with brain tumors and abscesses. Vasogenic edema can be localized or diffuse, depending on the etiology. When the edema is localized, focal neurologic signs may be seen. Vasogenic edema appears hypodense on computed tomography (CT) scan and has increased T2 and fluid attenuated inversion recovery (FLAIR) intensity on magnetic resonance imaging (MRI) scan. Treatment depends on the etiology; although steroids are ineffective for most types of edema, they are particularly effective for vasogenic edema related to primary or metastatic brain tumors.

Cytotoxic edema results in cellular swelling (expansion of the intracellular space). This may be due to cellular entry of sodium and water when ion pumps fail, as typically occurs with ischemia (Chapter 71). It may also be due to the accumulation of osmotic particles within neurons and astrocytes, as may occur in fulminant liver failure (Chapter 59). Cytotoxic edema may affect the brain focally, as with acute ischemic stroke, or globally, as with cardiac arrest and liver failure. Cytotoxic edema also appears hypodense on CT scans. It may be distinguished from vasogenic edema on MRI scans by the presence of restricted diffusion (hyperintensity on diffusion-weighted sequences with hypointensity on apparent diffusion coefficient maps).

MASS LESIONS

Mass lesions are the most common cause of increased ICP. Mass lesions include intracranial tumors and hematomas, both of which may be either intra- or extracerebral, and brain abscesses. The ability to tolerate a mass lesion (and its effect on ICP) depends both on the speed with which it develops and its location. Slowly growing masses allow for compensation—CSF is more rapidly reabsorbed, compressed brain tissue loses intracellular and extracellular water and blood volume, and ICP can remain stable for a long time. However, hyperacute mass lesions, such as active bleeding, do not allow for compensation and ICP rapidly rises. Solid masses create displacements and stresses in nearby tissue that diminish with distance. Displacements that obstruct CSF flow are dangerous because they cause hydrocephalus, which adds to the mass burden. Displacements that cause tissue shifts from one intracranial compartment to another (herniation) are also dangerous and are covered in the next section. Treatment of life-threatening mass lesions is frequently surgical resection.

Herniation Syndromes

Because the adult skull is rigid, the intracranial compartment has a fixed volume that poorly accommodates acutely expansive processes. The cranial contents are further divided by semi-rigid dural reflections. The tentorium divides the posterior fossa (brain stem and cerebellum) from

the supratentorial compartment (cerebral hemispheres and diencephalon). The midbrain bridges these two spaces and is located at an opening in the tentorium, the incisura. The falx cerebri separates the two cerebral hemispheres.

Shifts of brain tissue from one compartment to another (herniation) are caused by intercompartmental pressure differences and result in characteristic clinical syndromes. Mass lesions in the temporal lobe may result in lateral displacement and herniation of the uncus (medial temporal lobe) through the tentorial incisura resulting in midbrain compression. In the uncal herniation syndrome, patients exhibit early deterioration in consciousness, ipsilateral pupil dilation and ptosis (third nerve palsy), and contralateral (or occasionally ipsilateral) hemiparesis accompanied by upper motor neuron signs. As the midbrain is further compressed, a progression of signs and symptoms are often observed including an oscillatory ventilatory pattern (Cheyne-Stokes breathing), coma progression, decerebrate posturing, and eventual loss of the oculocephalic reflexes.

Large frontal or parietal mass lesions may exert downward (vertical) force and cause central herniation of the diencephalon and midbrain through the incisura. Classically the central herniation syndrome involves an orderly progression of signs that indicate progressive rostral to caudal brain dysfunction. Early signs result from compression of the diencephalon and include confusion, decreased level of arousal, Cheyne-Stokes respirations, small (but reactive) pupils, decorticate posturing, and roving eye movements. As the midbrain is compressed, the pupils become midsized and nonreactive. Once the pons becomes dysfunctional, the breathing pattern may change to hyperventilation and then to apneusis (deep, gasping inspirations with end-inspiratory breath holding), and ultimately decerebrate posturing is observed. Late in the course of central herniation, the oculovestibular (cold caloric) and oculocephalic (doll's eyes) reflexes are lost, breathing becomes ataxic (irregularly irregular), and finally, as the medulla is compressed, respirations cease. Central herniation, uncal herniation, and upward herniation of the cerebellum and midbrain through the incisura (occasionally seen with cerebellar mass lesions) all represent variants of transtentorial herniation.

Mass lesions in the frontal lobe may cause lateral displacement of the medial frontal lobe (cingulate gyrus) under the falx. The resulting subfalcine (cingulate) herniation syndrome is characterized by contralateral or ipsilateral leg weakness. This is due to compression of the medial motor cortex, or when severe, compression of ipsilateral or contralateral anterior cerebral arteries, which results in ischemia and ultimately infarction of the medial portion of the motor strip.

Mass lesions in the cerebellum may cause downward displacement of the inferior cerebellum (cerebellar tonsils) through the foramen magnum. Tonsillar herniation results in sudden respiratory arrest as the medulla is compressed ("talk and die" syndrome).

Clinical Approach

DIAGNOSIS

A brief history will generally point the examiner toward a cause (trauma, meningitis, shunt malfunction, etc.). Physical examination should always begin with obtaining vital signs. Hypertension and bradycardia (Cushing reflex) might indicate medullary compression from herniation. Profound hypertension usually accompanies most forms of intracerebral hemorrhage, regardless of the patient's baseline blood pressure. A neurologic examination must be performed and typically incorporates a scale of disease severity (e.g., Glasgow Coma Scale score). On funduscopic examination, the presence of papilledema suggests intracranial hypertension, whereas its absence does not exclude it. Conversely, the presence of spontaneous venous pulsations in the retina suggests normal ICP, whereas their absence provides little information. Forced downgaze ("sunset eyes") implies compression of the dorsal midbrain and may be seen with hydrocephalus and with tumors in the pineal region. Other significant findings have been previously discussed (see "Herniation

Syndromes," presented earlier in the chapter). The level of consciousness typically dictates the therapeutic urgency. Comatose patients, especially with signs of herniation, require immediate (empiric) treatment, typically with hyperventilation and mannitol, prior to a diagnostic CT scan. A noncontrast CT scan of the head is usually the diagnostic test of choice in an emergency situation because it is relatively quick compared to an MRI scan and has a high sensitivity for intracranial bleeding. Findings on CT scan that raise suspicion for intracranial hypertension include large mass lesions, especially if deemed acute, evidence of tissue shifts (herniation), and findings suggestive of cerebral swelling including effacement of the basal cisterns (CSF spaces around the base of the brain), flattening of the cerebral sulci, blurring of the differentiation between gray and white matter, and large hypodense areas consistent with cerebral edema.

To definitively establish the diagnosis of intracranial hypertension, ICP must be measured. This may be done via lumbar puncture (LP) or via an ICP monitor. Lumbar puncture is contraindicated if a large mass lesion is present and in patients with bacterial meningitis who have a rapidly declining level of arousal. In these settings, LP may precipitate herniation. The gold standard for direct and continuous ICP measurement is the ventriculostomy, or external ventricular drain (EVD), a flexible, fluid-filled catheter inserted through brain tissue and into the ventricle and coupled to a pressure gauge. Fiberoptic intraparenchymal catheters, placed through a bolt into brain tissue, also allow for continuous ICP monitoring. Other, less frequently used locations in which catheters can be placed to transduce pressure include the epidural, subdural, and subarachnoid spaces.

THERAPY

Initial therapy of intracranial hypertension is often empiric. As for all critically ill patients, initial efforts are directed at stabilizing airway, breathing, and circulation. If a large, surgically accessible mass lesion (e.g., subdural or epidural hematoma) is causing life-threatening intracranial hypertension, then immediate surgical evacuation is paramount. Postoperatively, and in less emergent settings, specific therapy for intracranial hypertension traditionally follows a stepwise approach (Figure 41.3).

Several basic maneuvers ("universal measures") should be taken initially in all patients. These include positioning the patient with head of bed upright and neck straight. Endotracheal tube (or tracheostomy) ties and the cervical collar are inspected to ensure that they are not compressing the jugular veins. Measures to reduce unnecessary increases in cerebral metabolic demand are taken, including treatment of pain, agitation, fever, and seizures. If the patient is actively herniating, then immediate hyperventilation should be employed. Hyperventilation causes cerebral vasoconstriction, which reduces cerebral blood volume and hence ICP. However, it may also reduce cerebral

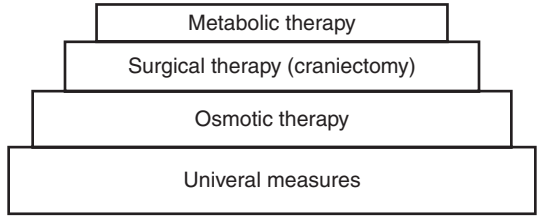


Figure 41.3 Stepwise approach to management of intracranial hypertension. Management of intracranial hypertension typically proceeds in steps starting at the base and moving upward stepwise on an as needed basis. Universal measures are employed in all patients, followed by osmotic therapy, surgical therapy, and metabolic therapy as needed. Cerebrospinal fluid (CSF) diversion and emergency hyperventilation may be used at any stage of therapy. See the text for details.

blood flow to ischemic levels and should only be employed as a temporary emergency measure until more definitive therapy is available.

If universal measures prove ineffective, an osmotic agent is administered. The two most commonly used agents are mannitol and hypertonic saline. A 20% or 25% solution of mannitol is typically given as a 1 g/kg IV bolus. It should be administered through a filter to prevent precipitated material from entering the vein. Side effects of mannitol include intravascular volume depletion and hypotension, renal failure, and rebound cerebral edema. To avoid dehydration and hypotension, urinary losses may be replaced with normal saline on a mL-per-mL basis. The risks of developing renal failure and rebound cerebral edema are likely related to the amount of mannitol that accumulates in the circulation. The osmolar gap (measured osmolarity—calculated osmolarity [see Chapter 83, Equation 5]) reflects serum mannitol accumulation (assuming no other exogenous source of osmoles). No further mannitol should be administered if the osmolar gap is excessively high (e.g., > 20). Hypertonic saline is commonly administered as a 3%, 5%, 7%, or 23.4% solution, either as a bolus or as a continuous infusion. Data are lacking with respect to the optimal dose and method of administration.

If osmotic therapy fails, then surgery, typically a craniectomy, should be considered. Removing the skull, either unilaterally or bilaterally, allows the brain to herniate through the craniectomy defect (transcalvarial herniation) rather than toward the brain stem. Surgery is unequivocally lifesaving and is the most effective means for lowering ICP. However, its impact on long-term outcome is controversial. Although data from a large pooled analysis support the use of craniectomy to treat malignant edema from large ischemic stroke, a 2011 study of craniectomy for swelling related to traumatic brain injury did not impart a survival benefit at 6 months.

If severe intracranial hypertension persists despite craniectomy, or if craniectomy is not feasible, then metabolic therapy is employed. Metabolic therapy aims to reduce cerebral metabolic demand to the greatest extent possible. This may be done by induction of pharmacologic coma, typically with anesthetic doses of intravenous (IV) barbiturates. The dose of drug should ideally be titrated to achieve an ICP < 20 mm Hg or an isoelectric (flat) electroencephalogram (EEG) tracing—whichever occurs first. Once the EEG is isoelectric, metabolic demand is assumed to be maximally suppressed and further increases in barbiturate dose predispose to complications. As an adjunct or as an alternative to pharmacologic therapy, mild to moderate induced hypothermia (32.0° C to 34.0° C) may be employed.

At any point in therapy, CSF diversion, typically through a ventriculostomy, may be used. Often removal of only a small amount of fluid will significantly lower ICP if the patient is on the steep portion of the intracranial compliance curve (see Figure 41.2). However, it may be very difficult to properly position an external ventriculostomy drain in patients with slitlike ventricles. Once intracranial hypertension has been established and its cause is known, further therapy is disease specific and should be managed with the assistance of a neurologist or a neurosurgeon.

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CHAPTER 42

Pressure Ulcers: Prevention and Management

Ave Maria Preston

Pressure ulcers (PUs) are a significant health problem in U.S. acute care facilities. Among all hospitalized patients, the highest prevalence of acquired pressure ulcers is in intensive care unit (ICU) patients, from 14% to 42%. An estimated 60,000 patients die each year from PU complications, denoting a poor overall prognosis.

PUs are painful, impair quality of life, and are expensive to treat. The Centers for Medicare and Medicaid Services (CMS) report that the cost of treating a single full-thickness PU in acute care is $43,180 per hospital stay. Increasingly, external regulatory agencies consider all PUs preventable, and CMS no longer reimburses hospitals for the added costs to treat hospital-acquired PUs.

Definition and Etiology

The National Pressure Ulcer Advisory Panel (NPUAP) and European Pressure Ulcer Advisory Panel (EPUAP) define pressure ulcers as "localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear." Unrelieved pressure leads to decreased tissue perfusion and ischemia, culminating in tissue damage and PU formation. Reperfusion, after prolonged ischemia, may increase the damage due to free radicals. In the presence of friction and/or shearing forces, PUs develop faster than under non-shearing conditions.

Although pressure is always a component factor, multiple other risk factors for PUs exist. Many of these other risk factors affect tissue tolerance, that is, the ability of the skin and soft tissue to absorb and tolerate mechanical load. Tissue tolerance is influenced by both extrinsic factors (e.g., moisture, friction/shear) and intrinsic factors (e.g., perfusion/oxygenation, nutrition, severity of illness, body habitus, edema and chemical exposure to fecal incontinence). The number and severity of intrinsic factors for tissue tolerance in critically ill patients may help explain the disproportionate incidence of PUs in this vulnerable population.

Staging

Pressure ulcers are classified based on the depth and layer of tissue involvement, typically in accord with the NPUAP classification system (see Table 42.E1). Historically, the term *stages* created a mistaken notion that all PUs commonly begin superficially (i.e., Stage I) and progress sequentially to the deeper Stages II, III, or IV. To the contrary, research using diagnostic ultrasound reveals that PUs begin with deep tissue injury moving from the bone outward.

The most common PU sites are the sacrum, heels, greater trochanter, and ischial tuberosity. Medical devices such as cervical collars; nasogastric, nasoenteral, and endotracheal tubes; Foley catheters; and non-invasive ventilation masks can also create pressure.

Additional online-only material indicated by icon.

TABLE 42.E1 ■ **National Pressure Ulcer Advisory Panel Pressure Ulcer Stages/Categories**

Category/Stage	Definition
Category/Stage I: Non-blanchable erythema	Intact skin with non-blanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its color may differ from the surrounding area.
	The area may be painful, firm, soft, warmer, or cooler as compared to adjacent tissue. Category I may be difficult to detect in individuals with dark skin tones. May indicate "at risk" persons.
Category/Stage II: Partial thickness	Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled or sero-sanguinous filled blister.
	Presents as a shiny or dry shallow ulcer without slough or bruising.* This category should not be used to describe skin tears, tape burns, incontinence, associated dermatitis, maceration, or excoriation.
Category/Stage III: Full thickness skin loss	Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon, or muscle are *not* exposed. Slough may be present but does not obscure the depth of tissue loss. *May* include undermining and tunneling.
	The depth of a Category/Stage III pressure ulcer varies by anatomic location. The bridge of the nose, ear, occiput, and malleolus do not have (adipose) subcutaneous tissue and Category/Stage III ulcers can be shallow. In contrast, areas of significant adiposity can develop extremely deep Category/Stage III pressure ulcers. Bone/tendon is not visible or directly palpable.
Category/Stage IV: Full thickness tissue loss	Full thickness tissue loss with exposed bone, tendon, or muscle. Slough or eschar may be present. Often includes undermining and tunneling.
	The depth of a Category/Stage IV pressure ulcer varies by anatomic location. The bridge of the nose, ear, occiput, and malleolus do not have (adipose) subcutaneous tissue and these ulcers can be shallow. Category/Stage IV ulcers can extend into muscle and/or supporting structures (e.g., fascia, tendon, or joint capsule) making osteomyelitis or osteitis likely to occur. Exposed bone/muscle is visible or directly palpable.
Unstageable/Unclassified: Full thickness skin or tissue loss — depth unknown	Full thickness tissue loss in which the base of the ulcer is covered by slough (yellow, tan, gray, green, or brown) and/or eschar (tan, brown, or black) in the wound bed.
	Until enough slough and/or eschar is removed to expose the base of the wound, the true depth cannot be determined; but it will be either a Category/Stage III or IV. Stable (dry, adherent, intact without erythema or fluctuance) eschar on the heels serves as "the body's natural (biological) cover" and should not be removed.
Suspected deep tissue injury — depth unknown	Purple or maroon localized area of discolored intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or *shear*. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer, or cooler as compared to adjacent tissue.
	Deep tissue injury may be difficult to detect in individuals with dark skin tones. Evolution may include a thin blister over a dark wound bed. The wound may further evolve and become covered by thin eschar. Evolution may be rapid exposing additional layers of tissue even with optimal treatment.

*Bruising indicates deep tissue injury.

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Risk Assessment and Prevention

A large number of factors influence an individual's risk to develop PUs. In critically ill patients, these risk factors are exaggerated. Formal risk assessment scales such as the Braden scale are widely accepted and recommended, but omit common ICU predisposing conditions such as intense vasoconstrictive drug therapy, hemodynamic instability, and mechanical ventilation (Table 42.1). Recommendations for preventing PUs start with identifying patients at risk and implementing prevention strategies (Table 42.2). Although there are clinical circumstances in which a pressure ulcer is unavoidable, PU incidence and prevalence can be reduced when evidence-based guidelines and bundles are rigorously used.

Repositioning

Frequent repositioning that minimizes exposure to both high degrees and prolonged durations of pressure is essential to prevention. Repositioning frequency will be determined by an individual's initial skin condition, tissue tolerance, level of activity and mobility, general medical condition, overall treatment objectives, and the pressure-redistributing qualities of the support surface.

TABLE 42.1 ■ **Risk Factors for Pressure Ulcers**

Risk Factors in Braden Scale	Risk Factors in the Critically Ill
Sensory perception	Duration of surgery
Immobility	Fecal incontinence and/or diarrhea
Activity	Low albumin
Incontinence	Altered sensory perception
Nutrition	Edema
Friction and shear	Skin moisture
	Impaired circulation
	Use of inotropic drugs
	Mechanical ventilation
	Diabetes mellitus
	Too unstable to turn
	Decreased mobility
	Multiple devices

TABLE 42.2 ■ **SKIN CARE© Bundle**

Support surfaces
Keep repositioning
Incontinence care
Nutrition and hydration
Careful lifting
Assess risk and skin daily
Reduce HOB ≤ 30° (unless contraindicated)
Elevate heels
SKIN CARE© Trustees of the University of Pennsylvania

Ultimately, clinical findings from daily skin inspection should guide repositioning frequency. Early skin changes (i.e., nonblanching erythema) are an important warning sign and support increasing repositioning frequency. One should initiate a turning schedule within hours of admission to the ICU. To reduce the risk of hemodynamic instability while turning a critically ill patient, preoxygenate before position changes, initially use the right lateral position to prevent the hemodynamic challenges reported with the left lateral position, reduce the speed of the turn, and wait 5 to 10 minutes after a position change to allow for equilibration before assessing patient tolerance to the position change. If the patient does not tolerate manual turning using these recommendations, consider the use of continuous lateral rotational therapy (CLRT) attempting to achieve tolerance of side-to-side movement.

While in bed, the lowest interface pressure patient positions are the 30° tilted side-lying position (alternating right side, back, left side), the 30° semi-Fowler's position, and the prone position, as allowed by the individual and his or her medical condition. Use of the prone position requires careful padding and positioning. Since raising the head of the bed (HOB) above 30° significantly raises interface pressure, and current guidelines to prevent ventilator-associated pneumonia (VAP) recommend a semirecumbent position with the HOB 30° to 45°, one should keep the HOB at 30° to manage the risk for both VAP and PU development. Also, one should pay special attention to reduce pressure and shear on the heels—for example, by using heel protector boots or by placing a pillow under the patient's calves to elevate or float the heels free of the bed surface.

Finally, one should limit the time patients spend seated in a chair without pressure relief (e.g., 2 hours or less). Also, one should employ seat cushions that provide pressure redistribution (but avoid the traditional donut-shaped cushion that actually increases PU risk).

Support Surfaces

Support surfaces are specialized pressure redistribution devices that manage tissue load and microclimate. Typical ICU support surfaces include powered air mattresses, low air loss beds, and air-fluidized beds. Insufficient evidence exists to definitively recommend one surface over another. Such specialty beds are expensive, and many hospitals have protocols to help maintain cost-effectiveness. Utilizing these alternative support surfaces should be considered for patients with poor local and systemic oxygenation and perfusion. Also, patients who cannot be positioned to lie off a PU, have PUs on two or more turning surfaces, or remain at high risk for additional PUs merit considering these alternative surfaces. Finally, deterioration or failure to heal a PU may warrant changing the existing surface. Regardless of the support surface in use, repositioning is still needed.

Beds with CLRT are used in the critically ill for helping to mobilize pulmonary secretions and to train the body to tolerate side-to-side movement. Friction and shear can occur with CLRT, which is not designed to replace repositioning and turning of the patient. One should position and bolster patients receiving lateral rotation to reduce friction and shear. At the first sign of tissue damage, one should consider discontinuing lateral rotation. Likewise, weigh the risks and benefits of CLRT should be weighed against causing a new, or worsening an existing, ulcer.

The use of beds with low air loss and air fluidized features improves healing outcomes for Stages III and IV ulcers. Low air loss therapy describes a support surface that lets air pass through the pores of the cover material, preventing buildup of moisture and subsequent skin maceration. Plastic underpads should be avoided on low air loss and air fluidized beds (e.g., Clinitron) to prevent blocking airflow. Multiple linen layers should be avoided on any support surface, which can increase interface pressure and temperature, moisture skin damage, and pressure ulcer development.

Moisture Management

Irritation or maceration resulting from prolonged exposure to urine, perspiration, and feces hastens skin breakdown. Moisture makes the skin more susceptible to damage from friction and

shear during repositioning. Therefore, maximizing effective treatment of incontinence and proper attention to skin care should reduce the occurrence of PUs. Skin care principles include (1) prompt cleansing with a mild pH-balanced cleanser after incontinent episodes, (2) moisturizing dry skin, and (3) applying a topical moisture barrier or alcohol-free liquid skin sealant. Active ingredients of the cream or ointment-based moisture barriers often include petrolatum, dimethicone, zinc oxide, or some combination of these ingredients. Zinc oxide ointment is the most effective barrier to liquid stool.

Selecting the most appropriate containment product can minimize contact with urine and feces. Indwelling urinary catheters are never indicated for long-term use in patients with urinary incontinence, but they can promote healing in patients with Stages III and IV PUs. Internal fecal containment devices (also referred to as fecal management systems [FMSs]—e.g., Flexi-Seal FMS, Convatec; Zassi Fecal Collector, Hollister) are effective, temporary devices for high-volume liquid diarrhea and fecal incontinence that reduce the risk of skin breakdown. A diverting colostomy may be necessary for nonhealing sacral or ischial Stage III or IV PUs, or prior to surgical flap closure.

Nutrition

Both poor nutritional intake and poor nutritional status correlate with the development of PUs as well as the delayed healing of wounds. All patients at risk for the development of PUs should receive a nutritional evaluation. A registered dietician should closely follow individuals with an existing PU and also patients at risk for PUs with poor nutritional status, to consider high-protein nutritional supplements. Adequate intake of calories, protein, and fluid is needed for both prevention and healing of PUs. Micronutrients "hypothesized" to promote PU healing include vitamin C, zinc, and copper. If normal feeding and oral supplements fail to meet the individual's requirements, other routes (for example, tube feedings) should be used (see Chapters 15 and 16).

Wound Bed Preparation

Wound bed preparation, represented by the acronym TIME, is a concept in chronic wound healing that focuses on debridement, bacterial balance, and management of exudate (Table 42.3). Removing nonviable tissue is essential for restoring viability to the wound base. Chronic wounds require ongoing maintenance debridement to continually allow healthy new granulation tissue to grow. There are five types of debridement: surgical, mechanical, enzymatic, autolytic, and biosurgery. For further description of types of debridement, refer to Table 42.4.

Although all chronic wounds are either *contaminated* or *colonized* with bacteria, wounds with significant bacterial burden or infection do not heal. *Critical colonization* occurs when an increasing bacterial burden delays wound healing. A wound is considered *infected* when bacteria invade the tissue, reproduce, and cause a host reaction. For signs of critical colonization versus systemic infection, refer to Table 42.5. One should suspect osteomyelitis if exposed bone is present.

TABLE 42.3 ■ **TIME Principles of Wound Bed Preparation**

Tissue—nonviable or deficient
Infection/**I**nflammation
Moisture imbalance
Edges of wound nonadvancing or nonmigrating

Systemic antibiotics should be reserved for those individuals with clinical evidence of infection, and target bacteria cultured from wound tissue (not the wound surface).

Saline is the solution of choice for wound cleansing. Application of antiseptics and antimicrobial topical agents is a common practice. However, balancing cytotoxicity from certain agents (hydrogen peroxide, povidone-iodine, Dakin's solution) with desired antimicrobial action remains challenging. One can consider the use of silver or medical-grade honey dressings for ulcers infected with multiple organisms, because they offer broad antimicrobial coverage.

Wounds heal best in a continuously moist environment. Avoid gauze dressings on clean, open PUs because they are labor intensive to use, cause pain if removed when dry, and desiccate viable tissue as they dry. Create the optimum wound healing environment by using advanced dressings (e.g., hydrocolloids, hydrogels, hydrofibers, foams, films, alginates and silcones) in preference to gauze. For guidelines for choosing advanced dressings, refer to Table 42.6. If moisture retentive dressings are unavailable, continually moist gauze (changed frequently) is preferable to dry gauze. Compared to conventional treatment, hydrocolloid dressings significantly improve PU healing rates. However, there are no significant differences between advanced dressings in healing rates.

If the epithelium at the wound edge fails to advance, reevaluate whether the barriers to healing have been adequately removed or there is a need for further wound bed preparation. Debridement of a hard, rolled wound edge, or undermining at the wound edge, may be needed to stimulate

TABLE 42.4 ■ **Types of Debridement**

Surgical	• fastest and probably most efficient method • should always be considered with cellulitis or sepsis
Mechanical (e.g., wet-to-dry gauze dressings)	• nonselective and can harm healthy granulation tissue, thereby delaying wound healing
Autolytic	• involves applying semiocclusive or occlusive moisture-retentive dressings (transparent film, hydrocolloids, hydrogels, etc.), which create an environment for the body's natural enzymes to slowly break down devitalized tissue
Enzymatic	• uses proteolytic enzymes (i.e., collagenase) to dissolve necrotic tissue • can be slow and costly
Biosurgery (maggot therapy)	• relatively uncommon in the United States • applies sterile larvae to the devitalized ulcer bed • larvae produce enzymes that break down necrotic tissue while sparing healthy tissue

TABLE 42.5 ■ **Signs of Critical Colonization vs. Systemic Infection**

Signs of Critical Colonization	Signs of Systemic Infection
• serous exudate	• fever
• friable granulation tissue	• pain
• a change in the color of granulation tissue to bright red	• erythema
• increasing pain	• edema
• increasing or unusual odor	• warmth
• wound breakdown	• purulent exudate

TABLE 42.6 ■ **Choosing Advanced Topical Therapy Based on Wound Management Goals**

Reduce friction
- Transparent film
- Foam

Add moisture to dry wound bed
- Hydrogel (amorphous and sheet)

Absorb exudate
- Hydrocolloid
- Calcium alginate (ropes and pads)
- Hydrofiber (ropes and pads)
- Foam

Decrease bioburden
- Silver impregnated dressings
- Medical grade honey dressings
- Cadexomer-iodine

Gentle adhesive
- Silicone-based dressings

Debridement
- Collagenase (enzymatic debridement)
- Medical grade honey dressings (autolytic and mechanical debridement)

Promote granulation tissue
- Negative pressure wound therapy (NPWT)

cell migration. Other treatments to consider include negative pressure wound therapy (NPWT), electrical stimulation, and skin grafting.

Negative Pressure Wound Therapy (NPWT)

Negative pressure wound therapy (NPWT) reduces the depth of PUs, compared to traditional topical therapies. NPWT promotes the removal of third space edema and excess exudate, granulation tissue formation, and angiogenesis. NPWT is used to treat deep, full-thickness (Stages III and IV) PUs, and contraindicated with untreated osteomyelitis, eschar, or exposed blood vessels or organs. The dressing is usually changed three times per week. If dressing change is painful, one should consider placing a nonadherent tissue interface dressing on the wound bed.

Prophylactic Dressings

One should consider using dressings to reduce pressure for body areas in contact with medical devices. The prophylactic use of a soft silicone border foam dressing may provide additional protection against friction, shear, and moisture, thus potentially reducing sacrococcygeal breakdown in high risk patients.

Pain

PUs are often painful. Possible strategies to address ulcer pain include choosing dressings that mitigate the pain associated with dressing changes (e.g., silicone foam dressings) and administering analgesics prior to dressing changes.

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CHAPTER 43

Skin Rashes

Misha Rosenbach

Primary dermatologic diagnoses rarely require admission to the intensive care unit (ICU), but many patients in the ICU develop dermatologic manifestations of their underlying disease or as complications of therapy. Dermatologic disorders complicate many ICU stays and prolong length of stay. This chapter describes a variety of benign and serious skin problems relevant to ICU patients and their physicians.

Common Benign Skin Rashes (Table 43.1)

CANDIDAL INFECTIONS

Candidiasis is most commonly caused by *Candida albicans* and occasionally by other candidal species. *C. albicans,* a yeast, inhabits the gastrointestinal tract, urinary tract, and intertriginous areas of the skin. The warmth and moisture of intertriginous areas provide a hospitable environment for growth. Higher skin pH, diapers, occlusive products, alteration of normal flora with systemic antibiotic use, and immunocompromised states all facilitate candidal overgrowth. *C. albicans* commonly infects the mucous membranes and skin, although in immunocompromised states there may be disseminated disease. In patients thus affected, untreated cutaneous candida infection may progress to widespread disease and even candidemia.

Candidal intertrigo occurs commonly and can involve any skin fold, especially in overweight individuals. Classically, the skin folds develop erythematous, beefy red patches, sometimes with an edge of macerated, superficially denuded skin. Frequently, tiny white pustules occur at the edges, and smaller red "satellite" lesions may be scattered just beyond the main rash. The skin lesions are painful when macerated and often pruritic.

When mucous membranes are involved, loosely adherent, creamy, well-demarcated curdlike debris on an erythematous base is typically seen on the tongue, buccal mucosa, gums, and palate ("thrush"). Oropharyngeal infection often progresses to involve the vermilion border at the angle of the mouth, causing maceration and fissuring known as perlèche. Severe mucosal candidal infection can extend to the esophagus and pharynx; esophageal candidiasis should prompt investigation of an underlying immunocompromised state—for example, as a presenting sign of human immunodeficiency virus (HIV) infection and representing an AIDS-defining illness. Treat oral candidiasis with anticandidal troches (clotrimazole), and intertriginous disease with topical creams (ketoconazole, econazole) twice daily. As intertrigo is frequently polymicrobial, topical therapy with soaks (acetic acid compresses), and keeping the area dry with barrier pastes (zinc oxide, triple paste) can be both therapeutic and preventive.

CONTACT DERMATITIS

Contact dermatitis occurs from the interaction of a chemical with the skin. There are two major forms: irritant and allergic. Irritant contact dermatitis accounts for 80% of cases and results from

damage to the skin via a toxic effect intrinsic to the compound; these irritants react with any skin and do not require prior sensitization. Common irritants in the ICU are soaps, stool, and urine, which when left in prolonged contact with the skin cause direct toxicity. These reactions typically occur within minutes to hours of the exposure, depending on the concentration of the irritant and the integrity of the skin.

TABLE 43.1 ■ **Skin Rashes**

Benign, Incidental, Common			
Name	**Cause**	**Clinical**	**Treatment**
Candidal skin infection	*Candida* spp.	Erythematous-to-red papules, confluent patches, often macerated, in skin folds, with "satellite" lesions at periphery	Topical antifungals—ketoconazole, econazole, clotrimazole, nystatin
Herpes simplex infection	Herpes simplex virus	Grouped vesicles on an erythematous base; vesicles may rupture and leave "punched out" erosions; may superinfect erosions and ulcers from other causes (e.g., physical/pressure ulcers)	Antivirals—acyclovir, valacyclovir
Zoster/shingles	Varicella zoster virus	Dermatomal eruption of vesicles and erythema, intense pain	Antivirals—acyclovir, valacyclovir
Contact dermatitis	External allergens or skin irritants	Geometric, sharply cut off eczematous patches or thin plaques; may exhibit bulla formation, often at sites of tape or skin preps	Avoidance of allergen/irritant; topical steroids, strength varies by site—hydrocortisone, triamcinolone
Miliaria	Physical pressure, heat, sweating	Red papules, often pruritic, on the back; usually seen in immobile, febrile patients	Frequent turning, cooling the room; consider topical antibiotics—clindamycin solution
Seborrheic dermatitis	Unknown, possibly yeast	Erythema and greasy scale over central face, scalp	Topical antifungals, occasionally supplemented with low potency topical steroids: — ketoconazole — hydrocortisone
Microvascular occlusion syndrome	Often caused by arterial lines or vasoactive medications	Lacy, reticulated violaceous patches (livedo reticularis)	Identify cause and evaluate extent; see text
Exanthematous drug eruption (morbilliform drug rash)	Cutaneous adverse reaction to medication	Blanching erythematous macules and papules, predominance on trunks, upper arms, sites of pressure and dependent areas	Evaluate for signs/symptoms of severe drug eruption; consider drug cessation/alternate agent

TABLE 43.1 ■ **Skin Rashes (Continued)**

Severe, Potentially Life Threatening			
Name	**Cause**	**Clinical**	**Treatment**
Drug rash with eosinophilia and systemic symptoms (DRESS)	Severe cutaneous adverse drug eruption	Widespread bright morbilliform eruption, usually involving face, with lymphadenopathy, hepatitis, complete blood count (CBC) abnormalities	Evaluate extent of internal involvement; dermatology consultation; systemic corticosteroids
Erythema multiforme minor	Usually reactive because of herpes simplex infection; rarely drug induced	Symmetric, acral target lesions often with mild mucosal involvement; herpes infection often identified	Examine patient for herpetic infection; rule out more severe reaction
Stevens-Johnson syndrome/toxic epidermal necrolysis	Severe cutaneous adverse drug eruption	Fever, mucositis, often conjunctivitis, cutaneous signs are variable from nonblanching purpuric macules to widespread targetoid lesions to large areas of desquamation, bulla, and necrosis	See text
Vasculitis	In the ICU, often because of infection or medication; underlying cause also may include connective tissue disease or malignancy	Nonblanching purpuric macules and palpable papules, often on distal sites, may be accentuated by pressure	Evaluate patient for extracutaneous involvement Attempt to identify trigger; dermatologic consultation; treatment depends on trigger and disease extent
Ecthyma gangrenosum	Infection, often *Pseudomonas*	Purpuric, nonblanching patch with central necrosis and bullae formation	Blood and skin cultures, broad systemic antibiotic therapy
Purpura fulminans	Overwhelming infection	Widespread nonblanching purpuric macules and patches, often with distal accentuation and distal necrosis with dusky, black skin and bulla formation	Identify causative organism and treat; patients often exhibit shock physiology and require multisystem support
Necrotizing fasciitis	Rapid subcutaneous infection, often but not always the result of streptococcal infection (Chapter 66)	Exquisitely painful, rapidly progressive, indurated skin lesions, which may be dusky, gray, and necrotic; key finding is pain out of proportion to exam	Immediate surgical diagnosis and intervention, antibiotics; patients often exhibit shock physiology and require multisystem support

Allergic contact dermatitis, a type IV cell-mediated delayed hypersensitivity immune response (see also Table 32.1 in Chapter 32), accounts for the other 20% of cases. It is antigen specific, and the reaction requires prior sensitization. In the ICU, patients may become sensitized to a variety of topical preparations, such as iodine, topical antimicrobials, or the adhesives used in tape or electrodes.

Generally, contact dermatitis appears as a well-demarcated, pruritic, erythematous, eczematous patch in a linear or geographic pattern corresponding to where the external agent was applied to the skin. Severe reactions can be vesicular or bullous in nature. Detection of the causative allergen can be determined by patch testing or by a "use test," applying the agent in question several times daily for 5 to 7 days to an unaffected area of skin in an attempt to invoke the reaction. Treatment is avoidance of the causative allergen or irritant and midstrength topical steroids, such as triamcinolone ointment 0.1%, for mild cases and more potent topical steroids, such as clobetasol propionate ointment 0.05% or betamethasone dipropionate 0.05%, for severe reactions. Topical treatment is twice daily for 10 to 14 days. Rarely, systemic steroids are required for extensive severe contact allergy. Conditions that fail to respond to therapy should prompt consideration of alternate diagnoses.

HERPES SIMPLEX VIRUS SKIN INFECTIONS

Herpes simplex virus (HSV) is a common acquired infection caused by HSV type 1 or 2. Clinically, HSV appears as grouped vesicles on an erythematous base, especially in the perioral or genital areas. As the infection progresses, the vesicles may be lost, and the morphology instead consists of numerous "punched out" shallow erosions, often with a distinctive scalloped border. This acquired infection often recurs after trauma, ultraviolet light exposure, illness, or stress, as the virus infects nerves and lays dormant. Patients describe burning, itching, or stinging, which frequently precedes clinical lesions.

Diagnosis is made by Tzanck smear revealing multinucleated giant cells with nuclear molding, or by direct fluorescent antibody (DFA), polymerase chain reaction (PCR), or viral culture. In treatment-resistant cases, one should perform a viral culture to assess for drug resistance and guide therapy. Immunocompromised hosts may present with unusual morphologies and atypical lesions. HSV infection of the oral cavity may extend distally down the esophagus in intubated patients. HSV can occur at sites of pressure or trauma, such as around endotracheal or nasogastric tubes, and while erosions at those sites may be from physical causes, clinicians should consider whether viral superinfection may be present in atypical cases.

Topical treatment may reduce discomfort and promote healing; topical acyclovir, penciclovir, and tetracaine are variably efficacious. Oral acyclovir may decrease viral shedding, pain and crusting, and duration of disease if initiated early in the course of illness. In severe cases, such as most cases in the ICU or in immunocompromised patients, intravenous acyclovir may be used. Other antiviral options include famciclovir and valacyclovir. Resistant cases may require intravenous foscarnet or cidofovir.

HERPES ZOSTER

Herpes zoster, also known as shingles, is a vesicular eruption that occurs in a dermatomal distribution. Herpes zoster is caused by the reactivation of latent varicella zoster virus (VZV), which lays dormant in sensory neurons. Age and immunosuppression are the main risk factors for reactivation. The development of a zoster vaccine may eventually decrease cases in the elderly. Clinically, vesicles are seen on an erythematous base, distributed unilaterally in a dermatome, most commonly on the trunk (see Figure 101.1 in Chapter 101 for a discussion of sensory dermatomes). Occasionally the lesions become hemorrhagic; frequently they evolve to crusted erosions and then heal over the course of 2 to 3 weeks. Burning, stinging, itching, or pain often precedes the cutaneous manifestations. Up to 20 lesions can be found outside the affected dermatome, but a more extensive spread of lesions warrants prompt investigation for signs of *disseminated* varicella infection.

Initiate antiviral therapy as soon as possible, optimally within the first 72 hours of disease. Antiviral therapy promotes lesion healing and recovery, and it also decreases the risk of postzoster pain syndromes. Valacyclovir and famciclovir are preferable to acyclovir. Given that zoster is seen

frequently in elderly patients, appropriate dosing for age-adjusted renal function is essential. Local therapy with heat pads, pressure, and support may provide additional relief; and gabapentin use may reduce the risk of post-zoster pain. Intravenous therapy is occasionally necessary for the immunocompromised patient and is always required for disseminated disease.

MILIARIA

Miliaria results from obstruction of eccrine sweat ducts at various levels of the epidermis and dermis; as a result, sweat is retained in the skin. Miliaria crystalline manifests as asymptomatic, noninflammatory, small, fragile, superficial vesicles that rupture at the slightest contact. Miliaria rubra occurs as distinct, pruritic red papules and papulovesicles. Miliaria pustulosa consists of superficial, nonfolliculocentric pustules in intertriginous areas, on flexural surfaces, and on the back. These lesions may all appear after repeated episodes of fevers and sweating. Miliaria is fairly common in bed-confined ICU patients because of a combination of heat, moisture, and occlusion of the skin.

The cause of the obstruction is not clear. The condition resolves within days and treatment is symptomatic, keeping the area dry and unoccluded. Cooling the room or providing a fan for circulation, coupled with frequent turning and laundry changes, may help. Hydrophilic ointments or drying powders may also provide relief. Topical antibiotics, such as erythromycin or clindamycin, may also be used, as they may both dry out the skin and help to manage potentially causative microorganisms. Patients with severe pruritus may feel relief from short courses of mild- to moderate-strength topical steroids (triamcinolone ointment 0.1%).

SEBORRHEIC DERMATITIS

Seborrheic dermatitis is a common, benign papulosquamous disease. It affects sebaceous-rich areas such as the scalp, eyebrows, nasolabial folds, and central chest. Clinically, seborrheic dermatitis appears as erythematous macules and very thin plaques with greasy scale that can be pruritic.

The cause is unclear, but *Pityrosporum ovale,* a yeast found on normal skin and increased in seborrheic dermatitis, has been implicated. Seborrheic dermatitis flares in ill individuals and is associated with neurologic conditions such as Parkinson's disease or strokes, which may lead to unilateral seborrheic dermatitis on the affected side. Patients with HIV not only have a higher incidence of the disease but also have manifestations that are more extensive, severe, and resistant to therapy. The disease is chronic with a waxing and waning course. Treatment is with topical antifungal agents, such as ketoconazole cream twice daily, short courses of low-potency steroids (hydrocortisone ointment 1% or 2.5%) as needed, and medicated shampoos (selenium sulfide or ketoconazole).

Drug Reactions

Patients in the ICU typically receive multiple medications, placing them at risk for developing adverse cutaneous drug reactions. These reactions can range from common and relatively benign morbilliform eruptions to more serious and even life-threatening reactions such as erythema multiforme major or Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and drug-induced vasculitides. All cases of severe adverse drug reactions should be managed in conjunction with an experienced dermatology consultant.

MORBILLIFORM DRUG RASH

The most common drug reaction seen is a morbilliform eruption; this morphologic pattern comprises up to 90% of all cutaneous adverse drug reactions. Classically, patients present with

erythematous macules and papules. Lesions may exhibit preference for dependent areas and sites of pressure or friction such as elastic bands, adhesives, areas of skin-on-skin rubbing, and the sacral region. Mucosal surfaces should be examined for involvement, which may portend a more serious drug reaction.

This reaction typically takes place 4 to 14 days after starting a new medication and is presumed to be a type IV hypersensitivity reaction, although the immunologic pathophysiology has not been completely elucidated. A thorough query of the patient's medication history is essential to try to determine the most likely causative agent. Because it is difficult to identify the inciting agent accurately, discontinue any nonessential drugs. In limited eruptions with no concerning features (worrisome features include involvement of mucosal surfaces, skin pain, blistering, necrosis, or progression to involve sites typically spared, such as acral surfaces) some cases of morbilliform drug eruptions can be managed conservatively, and it may be possible to continue administering the causative agent if the implicated drug is essential to the patients' care. In the majority of cases, however, it is better to discontinue the suspect medication and note the allergy in the patient's medical record. One should perform daily cutaneous examinations to watch for progression. The drugs most frequently associated with morbilliform eruptions include allopurinol, aminopenicillins, cephalosporins, antiepileptic drugs, and antibacterial sulfonamides (see Chapter 32).

After discontinuing a suspected drug, the rash can worsen for a few days and persist for up to 2 weeks. Erythematous areas may exhibit superficial, nonpainful desquamation, resembling resolving sunburn. Symptomatic treatment of pruritus with topical midstrength steroids (triamcinolone ointment 0.1%) and lubricants (e.g., petroleum jelly, Absorbase) may be helpful.

DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

This severe cutaneous eruption encompasses entities previously known by a variety of names, including anticonvulsant hypersensitivity reaction. Patients with DRESS are often severely ill with multisystem disease, frequently requiring ICU admission. Patients present with a widespread morbilliform eruption, similar to that described previously. Notably, patients with DRESS typically exhibit facial involvement of the eruption, usually with edema; the presence of hand edema is noted in approximately one third of cases. Patients are often febrile (up to 40° C) and exhibit multiple laboratory abnormalities. Complete blood count often reveals a profound eosinophilia, but not all cases of DRESS require an elevated eosinophil count; many patients instead exhibit circulating atypical lymphocytes suggestive of a viral infection. Patients have systemic symptoms, which often include lymphadenopathy and internal organ involvement. Liver inflammation is most common, with marked hepatitis, and transaminase elevation can reach the thousands. Nephritis, pneumonitis, and myocarditis may be seen as well. All patients with DRESS should have close monitoring of liver function tests, serum creatinine, and a chest radiograph if pulmonary symptoms exist. Notably, because of the risk of myocardial involvement, patients should have an electrocardiogram (EKG), and some authors suggest all patients with DRESS warrant echocardiographic evaluation regardless of symptomatology.

DRESS is felt to be an immune reaction triggered by a medication, with a possible role for viral reactivation; the presence of numerous viruses, particularly human herpes virus 6, Epstein Barr virus, and cytomegalovirus has been documented. The most common triggers for DRESS are sulfonamide antibiotics, antiepileptic drugs, and allopurinol. Patients with DRESS require thorough evaluation for internal organ involvement and should be treated with systemic corticosteroids. Delayed sequelae may include cardiac involvement (which may be fulminant) or autoimmune phenomena (thyroiditis and diabetes).

ERYTHEMA MULTIFORME/STEVENS-JOHNSON SYNDROME

There is frequently confusion regarding the nomenclature and clinical distinctions between the various types of severe, bullous drug reactions. Erythema multiforme (EM) has traditionally been divided into EM minor, an acute, self-limited syndrome with mild, limited mucosal involvement; and EM major, characterized by significant mucosal involvement and epidermal detachment, and better known as Stevens-Johnson syndrome (SJS). EM minor is frequently associated with herpes simplex infection and may be more appropriately referred to as herpes-associated EM (HAEM). Both forms of EM can display typical targetoid lesions; however, the eruption can occur as macules, papules, vesicles, or bullae. The targetoid lesion is described as a "bull's-eye," with peripheral erythema and a central bulla or dusky necrotic center. EM minor typically affects only one mucosal surface, generally exhibits true target lesions symmetrically on acral sites, is most often associated with herpes simplex infection (occasionally with *Mycoplasma* infection), and tends to recur. EM major/SJS is almost always drug related and, unless patients are rechallenged with the causative agent, rarely recurs. In SJS, less than 10% of the skin surface exhibits epidermal detachment. Cases with greater than 30% epidermal detachment define toxic epidermal necrolysis (TEN). Cases with 10% to 30% epidermal detachment are considered overlap cases between SJS and TEN. SJS has an associated mortality of ~5%.

Patients with HIV have a higher incidence of severe adverse cutaneous drug reactions, for unclear reasons. SJS is rarely associated with infectious agents, but severe forms of HAEM and *mycoplasma*-associated SJS have been reported.

In HAEM, treatment of the underlying herpes infection is the mainstay of therapy; patients with recurrent disease may benefit from prophylaxis. Severe cases may require prednisone. In any cases of drug-associated EM, including SJS, the culprit drug must be stopped immediately. Stopping the causative agent within the first 24 hours of the skin beginning to blister yields less morbidity and mortality. These severe forms of drug reactions are multiorgan processes, and involvement of other systems should be assessed, examining all mucosal surfaces (including assessing for esophageal or tracheal involvement) and closely monitoring the liver and kidney function.

In limited cases, patients may be managed symptomatically with antihistamines for relief of pruritus, and moderate strength topical steroids (triamcinolone ointment 0.1%) as needed. Meticulous wound care is essential to prevent infection, with careful attention paid to all areas of blistered, denuded, dusky, or necrotic skin at risk for desquamating. Maintain intravenous access away from affected sites if possible, and avoid placing adhesives directly to affected skin. Hold any necessary dressings, leads, tubes, and lines in place by taping to wrapped gauze rather than placing the adhesive directly on the inflamed epidermis. Cover any erosions with moisture-retentive ointments such as plain white petrolatum or Vaseline-impregnated gauze. Reports suggest that bioengineered amniotic membranes may promote wound healing and reepithelialization. Closely monitor open areas of skin for colonization and infection, and some advocate routine bacterial sampling of skin lesions every 48 hours. Patients with widespread blistering drug reactions are at high risk of early *Staphylococcal* infection and later for *Pseudomonas* infections. There is no consensus on whether topical medications are useful; however, use silver sulfadiazine with caution because of the frequent association of sulfonamides with these severe forms of drug reactions. Manage painful mucosal erosions symptomatically with oral preparations of corticosteroids or viscous lidocaine. SJS and TEN frequently involve the ocular mucosa. The high proportion of patients experiencing prolonged sequelae from ocular complications warrants early consultation by an ophthalmologist.

Given the overlap between SJS and TEN, management of more severe cases of widespread blistering drug eruptions is described further, including the potential role of corticosteroids or intravenous immunoglobulin (IVIG) in the management of these patients.

TOXIC EPIDERMAL NECROLYSIS (TEN)

TEN is a drug hypersensitivity reaction resulting in more than 30% epidermal detachment at the most severe stage of the reaction. There is a 30% mortality associated with TEN. The SCORe of Toxic Epidermal Necrosis (SCORTEN) assessment scale can help physicians predict outcomes for patients. The medications most frequently associated with TEN are similar to those associated with SJS and include allopurinol, –oxicam nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, imidazole antifungals, sulfonamides, and other antibiotics. When patients experience either SJS or TEN, note an allergy to that compound in their medical record. Additionally, there may be a genetic predisposition to certain severe drug reactions, and first-degree relatives should be advised to avoid the causative agent.

Clinically, patients typically experience fever, conjunctivitis, pharyngitis, and pruritus, which may resemble an upper respiratory illness, before developing epidermal sloughing. Frequently the mucosae are affected first, followed by the skin. Patients may note painful skin, which can be erythematous or dusky and may show either typical targets or atypical targetoid lesions. The skin may become edematous and then develop widespread, flaccid blisters. The dusky skin is necrotic, and pressure or torsion of affected skin may induce or extend blisters, known as the Nikolsky sign. Skin biopsy with frozen section analysis provides rapid confirmation of the suspected clinical diagnosis and reveals full-thickness necrosis of the epidermis.

Patients will often have multisystem involvement and may develop anemia, cytopenias, and transaminitis. Because of the widespread epidermal loss, patients with TEN are managed like burn victims. These patients require temperature-controlled settings and aseptic sterile handling, with similar local care as described for patients with SJS (limit tape-to-skin, moisturize open areas, monitor for infection). Loss of the epidermis also destroys the skin's barrier function, and these patients lose large volumes of fluid through insensible losses. Intravenous fluid replacement may be estimated at two thirds to three quarters of what is required by burn victims. Early nutrition via Dobhoff tube may promote healing. Cases with extensive airway involvement frequently require intubation and mechanical ventilation. Because of the high risk of long-term ocular complications, early ophthalmic consultation is recommended. Involvement of the genital mucosa may require Foley catheterization, and even urologic consultation to decrease the risk of stricture formation. Mortality is high, often because of secondary infection and sepsis. One should consider transfer to a specialized burn unit for treatment. However, patients in such units should continue to receive dermatologic consultation and appropriate consideration to the use of indicated systemic medications.

Treatment options to manage these patients are controversial. Historically the mainstay of therapy, corticosteroid therapy has fallen out of favor. No randomized clinical trials exist, and primarily only case series, many of which have poorly defined comparison groups, guide current recommendations. Mechanistically, proponents note that corticosteroids decrease the immune response leading to the inflammatory hypersensitivity reaction, whereas opponents claim steroids suppress the compromised host and increase the risk of sepsis while delaying wound healing.

Other studies suggest a possible role for intravenous immunoglobulin (IVIG) therapy in the management of patients with severe cutaneous adverse drug reactions. Theoretically IVIG contains anti-Fas antibodies, which may inhibit the proapoptotic signal between Fas and Fas ligand on keratinocyte cell membranes. Limited current data suggest that high doses of IVIG reduce expected mortality in patients with TEN. Other treatment options reported include the use of cyclosporine or plasmapheresis.

VASCULITIS

Vasculitis may occur as a hypersensitivity reaction to medications; these reactions tend to have a good prognosis. Vasculitis secondary to drugs most often appears as palpable purpura on the

lower extremities. Diagnosis may be confirmed by skin biopsy or sometimes direct immunofluorescent examination of involved tissue. Patients with cutaneous vasculitis should be examined for other organ system manifestations, as mortality in these cases is associated with renal, gastrointestinal, pulmonary, cardiac, or central nervous system involvement. Although the exact mechanism is unknown, drug-induced vasculitis is felt to be immune mediated. Many drugs have been reported in association with vasculitis; the most commonly associated medications are antibiotics (particularly beta-lactam antibiotics), tumor necrosis factor inhibitors, colony-stimulating factors, minocycline, hydralazine, NSAIDs, and diuretics. Discontinuation of the drug generally results in resolution of the clinical findings. Therapeutic intervention may be necessary if other organ systems are involved.

MICROVASCULAR OCCLUSION SYNDROME

Lacy, reticulate purpura (livedo reticularis) favoring the distal extremities may occur because of low-flow states, vascular occlusion, systemic coagulopathies, and embolic processes. Skin lesions including cutaneous necrosis can follow this vascular process. Patients on vasopressive medications can develop retiform purpura, even progressing to ischemic necrosis of the skin. All patients in the ICU, particularly those receiving vasoactive medications, merit a thorough cutaneous physical examination, with particular care paid to the warmth, perfusion, and skin character of the distal extremities. Areas downstream of vascular access devices such as arterial lines may be at risk because of altered flow and a nidus for thrombus formation.

Life-Threatening Disorders Affecting the Skin

A number of life-threatening diseases may either manifest or initially present with dermatologic findings. Some primary dermatologic disorders can be deadly, such as autoimmune blistering diseases (pemphigus, bullous pemphigoid) and erythrodermic eruptions from causes ranging from acute flares of psoriasis to cutaneous T-cell lymphomas. Additionally, many rapidly progressive infections present with skin involvement, including staphylococcal toxic shock syndrome, staphylococcal scalded skin syndrome, angioinvasive fungal infections, and meningococcemia. Calciphylaxis or acute graft-versus-host disease may present with cutaneous findings and can be rapidly fatal. Retiform purpura may be a sign of numerous potentially deadly intravascular processes, ranging from septic/embolic infections, to catastrophic antiphospholipid antibody syndrome, to widespread fulminant cryoglobulinemic vasculitis/vasculopathy. Patients may present with extensive livedo racemosa and livedoid vasculopathy along with renal failure following endovascular instrumentation as a sign of cholesterol emboli. Although a thorough discussion of these entities is beyond the scope of this chapter, key information for the intensivist is presented regarding a few important, potentially life-threatening diseases with dermatologic manifestations.

ECTHYMA GANGRENOSUM

Ecthyma gangrenosum is an uncommon cutaneous finding that results from *Pseudomonas* sepsis and often occurs in immunocompromised individuals. Skin lesions are asymptomatic erythematous macules, which may progress to indurated, purpuric plaques and subsequently develop overlying bullae or eschar. Surrounding frank cellulitis occurs in some cases. Punch biopsy and culture can confirm the diagnosis, but immediate antibiotic therapy is essential in any suspected case.

PURPURA FULMINANS

Purpura fulminans is a rare, severe condition that results in hemorrhagic infarction and necrosis of large areas of the skin. Classically, purpura fulminans presents with symmetric, peripheral

gangrene. The cause is unknown, but most cases are associated with infections, with a minority attributed to underlying neoplasms. The implicated organisms include bacteria such as meningococci, group A streptococci, staphylococci, or pneumococci and occasionally viruses such as varicella. Disseminated intravascular coagulation (DIC) and depletion of coagulation factors are common associated findings. The clinical morphology may be confused with vasculitis, and dermatologic consultation can be critical in the diagnosis and management of these patients.

Patients acquire large, well-demarcated ecchymoses with associated hemorrhagic bullae located symmetrically on the extremities and pressure areas. A rim of erythema can surround these areas. Minor or insidious cases of purpura fulminans reveal petechiae, purpura, acral cyanosis, and hemorrhagic bullae. Affected patients are extremely ill with high fevers, tachycardia, and sometimes shock physiology. Laboratory studies reveal leukocytosis and changes indicative of DIC.

Mortality associated with purpura fulminans is high. Therapy includes treatment of infection or the underlying condition and sometimes replacement of clotting factors or plasma. Treatment with heparin to prevent clotting is occasionally used. Other therapeutic options include plasmapheresis, IVIG, and plasma ultrafiltration. If possible, minimize the use of vasopressors as these may exacerbate the peripheral gangrene and lead to more extensive amputation. Likewise, defer amputation until the affected areas have demarcated and the acute process resolved.

NECROTIZING FASCIITIS

Necrotizing fasciitis is a rapidly progressive infection of the subcutaneous tissue compartments, with a high associated mortality (see Chapter 66). Rapid diagnosis and aggressive therapy are essential to the care of these patients. Patients present with tender, erythematous, indurated areas of rapidly progressive cellulitis. The skin may be rigid and exquisitely painful. The infection rapidly extends along fascial planes, and the initially involved regions may progress to a more gray-blue, violaceous, or necrotic color. Bullae may develop within these areas. Patients are systemically ill, with high fevers, rigors, leukocytosis, and signs of shock. Clinical suspicion, recognition, and immediate radiologic confirmation is critical in managing patients with possible necrotizing fasciitis.

Various pathogens associated with necrotizing fasciitis include group A streptococci, *S. aureus, Escherichia coli*, *Bacteroides,* and *Clostridium*, requiring empiric administration of broad spectrum antimicrobial therapy. Many cases are polymicrobial and occur most frequently on the extremities following surgical procedures or traumatic injury. Surgical debridement is essential, and patients may require amputation. IVIG has been used in some cases of streptococcal infection. Adjuvant therapy with hyperbaric oxygen may be considered.

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CHAPTER 44

Sleep Disturbances in the Intensive Care Unit

Richard J. Schwab ■ Nirav P. Patel[†] ■ Aharon E. Sareli

Multiple factors impact sleep patterns in the critical care setting. These include both environmental and non-environmental factors. A substantial body of literature illustrates the impact of disrupted sleep patterns on numerous physiologic and homeostatic mechanisms. Abnormal sleep can alter immune function, hormonal and metabolic pathways, neurocognition, ventilation, and pulmonary mechanics. Although not yet proven, it stands to reason that disrupted sleep patterns may directly impact the morbidity and mortality of critically ill patients. Furthermore, patients in the intensive care unit (ICU) frequently complain of disrupted sleep and identify sleep disruption as an important cause of distress. In this context it is important to strive for restorative sleep in the ICU, while understanding the practical barriers to achieving this goal.

Normal Sleep

Sleep is complex and is characterized by a variety of physiologic, behavioral, and electroencephalographic changes. Sleep has two distinct states: (1) nonrapid eye movement (NREM) sleep and (2) rapid eye movement (REM) sleep. The initiation of sleep occurs through NREM sleep. NREM sleep consists of three stages that encompass 75% of sleep per night. Each subsequent stage of NREM sleep represents a deeper sleep state so that arousal thresholds are lowest in stage 1 and highest in stage 3 (delta sleep). EEG delta waves have a frequency of 0.5 Hz to 2 Hz and a peak-to-peak amplitude of > 75 microvolts. *Sleep architecture* refers to the normal sequence and cycles of sleep stages. Sleep architecture changes with age and can be different among individual subjects. A "typical" adult passes through stages 1 through 2 and enters stage 3 sleep about 35 minutes after the onset of sleep.

Dreaming occurs primarily during REM sleep. This stage of sleep is characterized by increased central nervous system (CNS) metabolic activity, skeletal muscle atonia, episodic rapid eye movements, and an EEG pattern (low-amplitude fast waves) similar to wakefulness. Periods of REM and NREM sleep normally alternate throughout a night of sleep. REM sleep cycles typically occur every 90 to 110 minutes and last 10 to 30 minutes. REM sleep cycle duration increases as one progresses through the normal period of sleep. Under stable conditions, REM sleep usually occurs in four to six separate episodes. In total, REM sleep comprises 25% of the total sleep time. The restorative properties of sleep depend on the duration and continuity of sleep and its architectural components (in particular achieving REM and delta or slow wave sleep).

The physiologic function of sleep remains unknown. However, evidence suggests that it may be needed for normal growth and repair of body tissues. It is suspected, but not proven, that sleep deprivation impairs healing and recovery. In most tissues, peak rates of protein synthesis and cell division coincide with sleep. Hormones that inhibit protein synthesis, such as cortisol and

[†]Deceased.

catecholamines, remain low during most of the night (when there is a normal circadian variation). Sleep is the normal stimulus for the release of the majority of growth hormone. In contrast, degradative metabolism is greater during wakefulness, and prolonged sleeplessness promotes a catabolic state. Sleep deprivation may impair all these physiologic functions. In fact, animal studies have shown that 2 to 3 weeks of total sleep deprivation in rats ultimately leads to death.

Sleep Patterns of ICU Patients

Polysomnography is the current objective gold standard for determining sleep architecture in the ICU. The polysomnogram (PSG) combines a recording of multiple EEG tracings with the measurement of other parameters such as oxygen saturation, respiratory rate and effort, as well as oral and nasal airflow. However, several aspects of polysomnography make it a challenging test to perform in the ICU setting. Additional monitoring of patients is required. Urgent testing or procedures frequently require patients to be transported out of the ICU. ICU equipment may interfere with polysomnographic recordings. The interpretation of EEG data, and hence sleep staging, is difficult in sedated or paralyzed subjects. Despite these significant limitations, polysomnography remains the best available objective method for obtaining data regarding sleep patterns in the critical care setting.

Studies of patient's sleep patterns in medical and surgical ICUs (using polysomnography) have demonstrated severe sleep deprivation (decreased total sleep time at night) and profound sleep fragmentation (loss of normal sleep architecture). These changes have been demonstrated in many ICU settings—for example, after myocardial infarction, general surgery, or open-heart surgery. Repeated arousals (awakenings or changes in sleep states to very light sleep) have been found to occur as often as every 20 minutes. These arousals disrupt the normal continuity of sleep stages and prevent achievement of the deepest stages of sleep (delta sleep and REM sleep). Most patients in the ICU are at high risk for being sleep deprived and having circadian dysrhythmia. For example, ICU patients experience only 50% to 60% of their sleep during nighttime hours. To compensate for this relative nocturnal sleep deficit, these patients often sleep during the day. Therefore, it is important to monitor sleep over a 24-hour period (not just at night) when examining sleep patterns in the ICU. This information can be challenging to obtain unless staff are vigilant of sleep patterns.

Factors That Contribute to Sleep Deprivation and Fragmentation in the ICU

Myriad factors interact to disrupt sleep in the ICU (Table 44.1). While many of these factors are non modifiable, others, such as ambient light, noise, timing of patient procedures, and certain medications, can be modified to decrease sleep disruption.

AMBIENT NOISE

Noise is a pervasive feature of hospitals, especially ICUs. ICU noise levels in the range of 60 to 84 dB have been documented. As a reference, a typical busy office environment's noise level would be approximately 60 to 70 dB. The alarm denoting the arrival of a pneumatic tube canister may generate 85 dB. Both baseline ambient noise levels and noise peaks are important. Noise peaks can cause arousals and disrupt sleep while loud background noise can act as a barrier to sleep initiation and maintenance. Studies have not yet determined if background noise or peak noise is more detrimental to restorative sleep. Studies that have correlated noise levels to polysomnographic recordings of sleep in the ICU have shown that noise accounts for approximately 17% of all arousals and 24% of awakenings. Although these data suggest that other factors contribute to sleep disruption in the ICU, noise reduction presents one opportunity to facilitate more consolidated sleep. Noise levels account

TABLE 44.1 ■ **Factors That Contribute to Sleep Disruption in Patients in the Intensive Care Unit (ICU)**

Patient Factors	Environmental Factors
Preexisting Primary Sleep Pathology	***Ambient Noise***
Obstructive or central sleep apnea (Chapter 80)	Equipment alarms
Obesity hypoventilation syndrome (Chapter 80)	Conversation
Restless legs syndrome and periodic limb movements	Pagers
Parasomnias	Television
Hypersomnia (e.g., narcolepsy)	Monitoring equipment
Patient Symptoms	Ventilator alarms
Pain	***Ambient Light***
Anxiety	Overhead lights
Agitation	Television
Fear	Monitoring equipment
Underlying Disease Process and Treatment Modalities	***Procedures and Patient Interactions during Night or When Patient Is Asleep***
Severity of illness	Phlebotomy
Metabolic derangements associated with illness	Bathing
Treatment modalities	Vital signs
—Medication effects	Medication administration
—Dialysis, etc.	Diagnostic studies at bedside and outside of the ICU
Ventilation and mode of ventilation	

for a greater degree of sleep disruption in healthy volunteers compared to ICU patients, suggesting that ICU patients may acclimatize to ICU noise with ongoing exposure. The use of patient earplugs is a low cost, practical intervention that is acceptable and comfortable for patients. ICU personnel need to be cognizant of the impact of noise on patients' sleep and should make efforts to minimize nocturnal noise. The provision of single-patient rooms and attention to positioning of monitoring alarms outside of patient's room are other effective strategies to reduce noise. Bedside devices that are noisy (such as nebulizers and infusion pumps) should not be placed at the head of the bed if feasible. Periodically, ICU noise levels should be monitored as part of a quality control initiative.

AMBIENT LIGHT

Although patients have identified noise as being more disruptive to sleep than light levels, light can also disrupt sleep in the ICU. Because the circadian rhythm is very sensitive to light and variation in light levels for synchronization, it is plausible that alterations in light levels in the ICU can impact a patient's sleep pattern. However, there have not been any studies that have correlated regulation of light levels and their impact on sleep (with sleep objectively measured by polysomnography). Even though such data are not available, it is prudent to try to maintain a patient's normal light-dark cycle and circadian rhythm while in the ICU. Attention to room design can helpful. For example, dimmer switches can facilitate a dark environment during nighttime. Similarly, windows permit exposure to natural light during daylight.

PROCEDURES AND PATIENT INTERACTIONS

Patient care activities have been shown to account for approximately 20% of patients' arousals during sleep (measured by polysomnography). Patient interruptions can often be decreased by

BOX 44.1 ■ Practical Measures to Improve Sleep Quality in Intensive Care Units

Light

- Place patients in rooms with windows to maximize natural light during daytime hours.
- Use dimmer switches in rooms to allow a dark environment at night.

Noise

- Use noise monitors to increase staff awareness of noise levels.
- Avoid unnecessary conversations at patient's bedside (e.g., rounding at night and teaching at bedside).
- Move audible equipment alarms outside of patients' rooms.
- Consider telemedicine to monitor patient's vital signs and alarms.

Procedures and Patient Interruptions

- Group procedures at same time of day, if timing is of no clinical importance.
- Avoid unnecessary interruptions to patient's sleep at night (e.g., for routine blood draws).
- Consider telemedicine to check on alarms and minimize multiple physical checks on patients.

bundling multiple interventions simultaneously (e.g., routine vital signs, radiographic studies, and morning phlebotomy). Furthermore, these interventions should take place between 5 and 6:30 a.m. when possible, rather than between 3 and 5 a.m. Routine nursing care should be evaluated for necessity and timing. For instance, the non-urgent administration of oral medication can be deferred for 1 to 2 hours if it can avoid disruption of a sleep period. Similarly, assessment of vital signs may not be indicated as frequently in a stable ICU patient. Telemedicine and remote patient monitoring is a promising development that may also help to minimize disturbed sleep and patient interruptions. Box 44.1 lists practical nonpharmacologic recommendations intended to facilitate restorative sleep in the ICU.

MEDICATIONS IN THE ICU

Commonly used medications in the ICU have an impact on sleep architecture. Nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, selective serotonin reuptake inhibitors (SSRIs), and theophylline decrease total sleep time. In contrast, benzodiazepines, propofol, chloral hydrate, risperidone, and haloperidol increase total sleep. Decreased REM sleep is noted with the use of benzodiazepines, dexmedetomidine, tricyclic antidepressants, SSRIs, trazodone, beta-agonists, vasopressors (epinephrine, norepinephrine, and dopamine), and corticosteroids. Slow wave sleep is decreased with the use of vasopressors (epinephrine, norepinephrine, and dopamine), benzodiazepines, opioids, and steroids. Although medications commonly used in the ICU have an impact on sleep, it is often not possible to choose alternatives (e.g., vasopressors).

Consequences of Sleep Deprivation

IMMUNE FUNCTION

There is a growing body of literature to support the notion that sleep deprivation can lead to impairment of host defenses and the immune system. Interestingly, sleep deprivation may suppress some elements of the immune system while stimulating others. Decreased numbers of natural killer cells, reduced cytotoxicity, and decreased interleukin-2 levels have been described after a single night of moderate sleep deprivation in healthy human volunteers. Inflammatory markers such as TNF-α (tumor necrosis factor-alpha), CRP (C-reactive protein), and IL-6 (interleukin-6) have been shown to be elevated in response to sleep deprivation. Moreover, adult patients subjected to

sleep deprivation have demonstrated an impaired response to influenza vaccination. Although multiple studies have shown changes in the immune system in response to sleep deprivation (including changes in cell-mediated immunity and interleukin levels), a causal relationship between sleep deprivation and disease state has not been clearly established.

HORMONAL AND METABOLIC PATHWAYS

The endocrine system is particularly sensitive to changes in sleep and circadian rhythms. Prolactin levels and growth hormone levels increase with sleep and are profoundly decreased in the absence of sleep. Sleep debt as a result of sleep deprivation is associated with decreased glucose tolerance, elevation in evening cortisol, and decreased thyroid-stimulating hormone (TSH) levels. Increases in sympathetic tone, norepinephrine levels, and cortisol levels occur with sleep deprivation. Robust changes occur in the endocrine system during periods of sleep deprivation and during sleep. These changes may contribute to the course of clinical critical illness and possibly to mortality. However, further data are needed to better correlate changes in the endocrine system with disease state outcomes.

NEUROCOGNITION

Delirium, a common ICU condition, is associated with increased morbidity and mortality, higher costs, and increased hospital length of stay. It is defined as an acute state of confusion, fluctuating mental status, and cognitive impairment (see Chapter 37). The prevalence of delirium ranges from 11% to 80% depending on the type of unit and population group. Sleep deprivation may be a factor that precipitates delirium in the ICU. Sleep-deprived healthy volunteers exhibit attention deficits, reduced response times, impaired memory, and other compromised aspects of cognitive function. As there is a clear overlap between the symptoms that are caused by sleep deprivation and those of delirium, it is feasible that a link exists between delirium and sleep disruption. Therefore, sleep deprivation should be avoided in all ICU patients and especially in those at risk for delirium. However, exploration of this potential relationship needs further study.

VENTILATION AND RESPIRATORY FUNCTION

In the context of critically ill patients, the impact of sleep deprivation on ventilation becomes particularly relevant. During sleep, chemoreceptors and respiratory reflex feedback mechanisms are the primary controllers of breathing. Early studies suggested that the ventilatory response to hypercapnia and hypoxemia was reduced after sleep deprivation. However, more recent literature has challenged this notion. A study of healthy non obese volunteers revealed no changes in spirometry after 24 hours of sleep deprivation. Similarly, in another study, 30 hours of sleep deprivation did not alter spirometric volumes (i.e., FEV1 and FVC) values but showed reduced inspiratory muscle endurance (calculated as a reduced product of inspiratory muscle load and sustained time). It is important to consider that these studies were performed in healthy volunteers; therefore, the findings are not directly applicable to ICU patients. The exposures that ICU patients' experience on a daily basis are vastly different and include acute and chronic cumulative sleep disruption, acute disease process(es), chronic disease(s), and medication side effects. In the ICU setting, sleep disruption may lead to compromised weaning of mechanically ventilated patients.

Few studies have attempted to investigate the effects of modes of mechanical ventilation on sleep patterns in the ICU. Because of confounding variables, small study populations, and practical study design limitations, specific modes of mechanical ventilation—conducive to improved sleep—cannot be recommended.

Use of Hypnotics in the ICU

Hypnotics are medications primarily intended to facilitate sleep. An ideal hypnotic would have (1) a short half-life (so that its sedating effects would not last beyond the normal sleep period), (2) no drug-drug interactions, (3) minimal effects on the cardiovascular or respiratory system, (4) no influence on normal sleep architecture, (5) absence of tolerance to its continued administration, and (6) no rebound insomnia on its cessation. Unfortunately, such a drug does not currently exist. All hypnotics have some degree of unwanted side effects. The Society of Critical Care Medicine recommends the use of nonpharmacologic measures and environment optimization to facilitate sleep—using hypnotics as adjuvant treatment.

ICU patients are a diverse group that requires different approaches for achieving sleep. For instance, mechanically ventilated patients often require anxiolytics and analgesia to facilitate safe ventilation and patient comfort. In this patient group, hypnotic action is a "side effect" of the medications used rather than their primary intent (see Chapter 5).

Currently, no data exist to justify the use of one hypnotic versus another in the critical care setting. Various hypnotic regimens have not been compared or even studied specifically in the ICU. Well-designed ICU trials comparing hypnotic drugs' effect on sleep architecture, efficacy, side effects, and safety profile are needed. Until these data become available, it is reasonable to base decisions on data derived from studies intended to evaluate sedation regimens in the ICU. Although useful, it is important to consider that such studies (including drug dosages) are designed to achieve effective sedation rather than restorative sleep.

BENZODIAZEPINES

Benzodiazepines are probably the most commonly used drugs with hypnotic properties in the ICU. These drugs affect sleep architecture by decreasing sleep latency and increasing total sleep time (primarily stage 2 sleep). However, benzodiazepines also cause a *decrease* in REM sleep and slow wave sleep. Common benzodiazepines used in the critical care setting are temazepam (Restoril), triazolam (Halcion), midazolam (Versed), and lorazepam (Ativan). In addition to their hypnotic properties, benzodiazepines induce amnesia, anxiolysis, sedation, and muscle relaxation. Unwanted side effects include respiratory depression, upper airway muscle hypotonia, next-day somnolence, headache, nausea, diarrhea, and possible hypotension. Intravenous and oral formulations are available.

NONBENZODIAZEPINE HYPNOTICS

Zolpidem (Ambien), *eszopiclone* (Lunesta) and *zaleplon* (Sonata) (so-called Z-drugs) are chemically unrelated to benzodiazepine but bind to the $GABA_A$ receptor (traditional benzodiazepines bind gamma-aminobutyric acid [GABA] receptors nonselectively). Unlike traditional benzodiazepines, zolpidem and the others do not alter sleep stages (preserving stage 3 and REM sleep). It is believed that the drug's specificity for the $GABA_A$ receptor is responsible for less cognitive impairment, memory loss, and reduced rebound insomnia. Only oral formulations are available. Dose adjustment is recommended in the presence of hepatic impairment, but no adjustment is required in renal disease. Side effects may include parasomnias and unusual behavior. Unusual complex behaviors such as sleep walking, sleep talking, and even sleep driving have been reported with the use of zolpidem. There are no published clinical data that address the use of zolpidem in the critical care environment. Because reported side effects of zolpidem have included unusual behaviors during sleep, a concern is its potential for contributing to the risk of delirium development in the ICU.

ANTIPSYCHOTIC MEDICATIONS

Antipsychotic medications such as trazodone, haloperidol, and quetiapine (Seroquel) are often used to treat agitated patients in the ICU, data regarding safety and side effects in the ICU setting are lacking. Therefore, these medications need to be used cautiously as hypnotics.

Trazodone decreases wakefulness, sleep latency, and REM sleep while increasing total sleep time. The impact on slow wave sleep is uncertain. Serious side effects include hypotension and priapism.

Haloperidol decreases sleep latency and increases stage 2 sleep with no significant effect on slow wave sleep. Serious side effects are arrhythmias (including QTc prolongation), hypotension, akathisia, extrapyramidal action, neuroleptic malignant syndrome, and bronchospasm.

Quetiapine side effects include hypotension, leukopenia, lowering seizure threshold, and neuromuscular weakness.

OTHER DRUGS USED TO PROMOTE SLEEP

Chloral hydrate is a rapidly acting hypnotic that can cause CNS and respiratory depression at high doses. Patients often become tolerant to its use over time. Its use in patients with hepatic and renal failure is not recommended.

Tricyclic antidepressants and antihistamines (such as diphenhydramine) suppress REM, have long half-lives, and have anticholinergic action. Therefore, their use as hypnotics is discouraged.

Ramelteon (Rozerem) acts as a melatonin receptor agonist. It has minimal side effects and no next-day residual effects. However, it should not be used in patients with severe hepatic disease. Only an oral formulation is available. There are no published clinical studies that address the use of ramelteon in the ICU.

Conclusions

In both ventilated and nonventilated ICU patients, one should first attempt to promote restorative sleep by nonpharmacologic measures (Box 44.1). One should consider ventilated ICU patients separately from nonventilated ICU patients when considering pharmacologic measures to promote sleep. In the former, one uses sedative medications to facilitate safe, effective, and comfortable ventilation, while recognizing that these medications often have hypnotic effects. Although few studies have compared benzodiazepines, propofol, and dexmedetomidine as sedating agents or compared side effect profiles and rates of delirium (see Chapters 5 and 37), it appears that benzodiazepines, dexmedetomidine, and propofol are all appropriate choices for sedation in the ICU. Perhaps more important than the particular choice of agent is the implementation of sedation protocols with an ongoing assessment of minimum effective dosages titrated to desired outcomes. The question of how well, if any, these agents facilitate restorative sleep remains unanswered.

Likewise, in nonventilated ICU patients, no clinical trials address the use of hypnotic agents to facilitate restorative sleep. An ideal hypnotic for use in the ICU does not yet exist. If the decision is made to initiate a hypnotic, underlying disease (particularly respiratory, renal, and hepatic disease) as well as concomitant medications should affect the choice of hypnotic. Antihistamines, tricyclic antidepressants, opioids, and chloral hydrate are not recommended as primary hypnotics. A benzodiazepine such as temazepam may be used as a hypnotic in the nonventilated patient, using the lowest possible effective dosage. However, this recommendation reflects a consensus opinion and is not evidence-based.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 45

Thrombocytopenia

Rebecca Kruse-Jarres ■ Marc J. Kahn

Platelets are cell fragments derived from megakaryocytes in the bone marrow. Platelets initiate hemostasis by adhering to damaged vessels, forming a plug, and providing a surface for the coagulation cascade. Platelet counts normally vary between 150,000/μL and 450,000/μL. Platelet counts significantly < 150,000/μL constitute thrombocytopenia. The differential diagnosis of thrombocytopenia includes disorders resulting from (1) increased platelet destruction (on an immune basis or nonimmune basis), (2) decreased platelet production, and (3) sequestration of circulating platelets (Box 45.1).

Over 50% of patients in the intensive care unit (ICU) have decreased platelet counts, and most patients experience a platelet nadir around day 4 of the ICU stay. Increased mortality is seen in patients who develop moderate or severe thrombocytopenia (platelet counts < 50,000/μL), especially in patients whose thrombocytopenia persists for a prolonged time period.

BOX 45.1 ■ Differential Diagnosis of Thrombocytopenia

Disorders of Increased Platelet Destruction

Thrombotic Thrombocytopenic Purpura (TTP)

Non–immune-mediated destruction
- —Disseminated intravascular coagulation (DIC)*
- —Drug-induced (cyclosporine, mitomycin C)*
- —Infections*
- —Sepsis syndrome*
- —Mechanical destruction (e.g., extracorporeal circulation)*

Immune-mediated destruction
- —Antiphospholipid antibody syndrome*
- —Idiopathic (immune) thrombocytopenic purpura (ITP)
- —Drug-induced (e.g., heparin, penicillin)*
- —Posttransfusion purpura (PTP)*

Disorders of Decreased Platelet Production

Marrow infiltration
Drugs suppressing hematopoiesis*
Aplastic anemia
Viral infections

Disorders Caused by the Splenic Sequestration of Platelets

Hypersplenism*
Hypothermia

* *In the differential diagnosis of thrombocytopenia that develops while a patient is in the ICU.*

Before any therapeutic or management decisions regarding thrombocytopenia are made for an ICU patient, a careful review of the peripheral blood smear should exclude pseudothrombocytopenia. This occurs when platelets clump in the presence of the anticoagulant used in the blood collection tube. Although anticoagulant-initiated platelet clumping has an estimated incidence of only 0.1%, it is the most common cause of falsely low platelet counts. Automated cell counters do not count platelet clumps, resulting in fictitiously low reported platelet counts. Pseudothrombocytopenia is most common in samples anticoagulated with ethylenediaminetetra acetic acid (EDTA), but it also occurs with anticoagulants such as heparin or citrate. The true platelet count can be correctly estimated with a manual count on a finger-stick blood sample. Alternatively, an automated count on blood drawn in collection tubes containing anticoagulants other than EDTA may be attempted. Platelet clumping is of clinical importance only as a source of confusion with true thrombocytopenia.

Disorders of Increased Platelet Destruction by Nonimmune Mechanisms

THROMBOTIC THROMBOCYTOPENIC PURPURA

The prototypic disease for nonimmune platelet destruction is thrombotic thrombocytopenic purpura (TTP) (see Chapter 63). TTP is caused either by a congenital deficiency of von Willebrand factor cleaving protease or by auto-antibodies directed against the protease. The protease is encoded by the gene designated as ADAMTS 13. Patients with TTP present with the clinical pentad of fever, renal abnormalities, central nervous system disorders, thrombocytopenia, and microangiopathic hemolytic anemia (MAHA). MAHA is characterized by the presence of fragmented red cells, or schistocytes (Figure 45.1), caused by erythrocyte destruction in the microvasculature. Hemolytic uremic syndrome (HUS) shares pathologic features with TTP, but in HUS renal abnormalities are more pronounced. HUS is most often secondary to infection with Shiga toxin, producing organisms such as *Escherichia coli* O157:H7. The primary treatment for TTP is plasmapheresis (also known as apheresis) accompanied by glucocorticoids. The treatment of HUS is usually supportive. Patients with TTP become thrombocytopenic from activation of platelets caused by the presence of large von Willebrand factor multimers. This leads to intravascular platelet aggregation and ultimate clearance of circulating platelets from the circulation. Platelet transfusions in TTP have been associated with fatal outcomes, presumably from microthrombosis, and

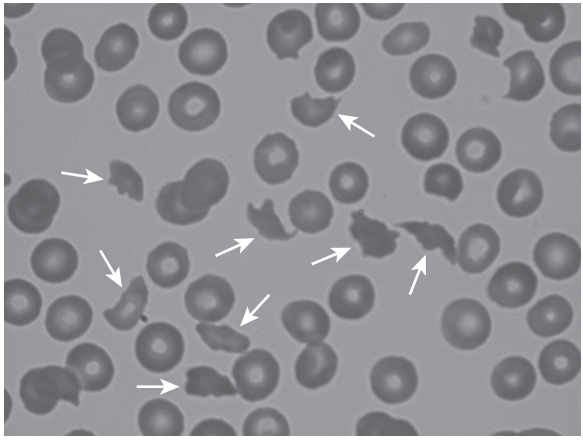


Figure 45.1 Microangiopathic hemolytic anemia is characterized by schistocytes *(arrows)* caused by erythrocyte destruction in the microvasculature.

are therefore contraindicated except for life-threatening bleeding. Fortunately, patients with TTP rarely bleed. Thrombocytopenia resulting from MAHA in conditions other than TTP usually responds to treatment of the underlying condition or removal of the offending drug (Box 45.2; see also Chapter 63). Again, as with classic TTP, there should be a reluctance to transfuse platelets in all but the most serious bleeding episodes.

DISSEMINATED INTRAVASCULAR COAGULATION

Thrombocytopenia in disseminated intravascular coagulation (DIC) is also secondary to platelet destruction. Much like TTP, in DIC, platelets become activated, clump, and are cleared from the circulation. Unlike TTP, ADAMTS13 is not responsible for platelet activation. Rather, thrombin deposition and the conversion of fibrinogen to fibrin lead to thrombocytopenia. In a large prospective, multicenter study, 8.5% of ICU patients were diagnosed with DIC, and the 28-day mortality rate was 21.9%.

DIC results from various causes, including gram-negative and gram-positive bacterial infections, trauma, snakebites, brain injury, and burns. In DIC, the generation of thrombin occurs without its subsequent neutralization, which is normally carried out by coagulation pathway inhibitors. Because thrombin promotes the conversion of fibrinogen to fibrin, microvascular thrombosis occurs. This results in tissue ischemia along with consumption of coagulation components such as platelets, fibrinogen, and prothrombin. DIC is often identified clinically by skin hemorrhage in the form of petechiae and ecchymoses. Alternatively, DIC can present as thrombosis of digits. Shock, organ dysfunction, and frank hemorrhage may occur as well. Other laboratory findings in DIC include prolongation of the prothrombin time, partial thromboplastin time, and thrombin time, a decrease in the fibrinogen level, and an increased level of fibrin degradation products (FDPs), also known as fibrin split products (FSPs). D-Dimers result from the degradation of cross-linked fibrin by plasmin, and their levels also increase in DIC. Primary fibrinogenolysis, a rare condition that results when plasmin is generated in the absence of DIC, is characterized by normal levels of D-dimers despite a low fibrinogen level.

BOX 45.2 ■ Drugs Commonly Associated with Thrombocytopenia

Drugs Inducing an Immune-Mediated Thrombocytopenia

Amrinone	Phenytoin
Aspirin	Procainamide
Cimetidine	Quinidine
Gold salts	Quinine*
Heroin	Ranitidine
Heparin	Rifampin
Indomethacin	Sulfonamides
Penicillin	Vancomycin

Drugs That Induce a Non–Immune-Mediated Thrombocytopenia

Increased Destruction (HUS-Like Syndrome)

Cyclosporine
Mitomycin C

Decreased Production

Many chemotherapeutic agents

* *Also produces a condition identical to HUS (hemolytic-uremic syndrome).*

One common clinical problem is differentiating DIC from the coagulopathy resulting from liver disease. In both conditions, fibrinogen is low, clotting times are prolonged, and fibrin degradation products are increased. Measuring levels of factors VIII and IX can help in distinguishing one from the other. Patients with DIC have consumption of all clotting factors and decreased levels of both factors VIII and IX. In contrast, because factor VIII is stored in endothelial cells, patients with liver failure have low factor IX levels but may have normal levels of factor VIII. Although schistocytes can be seen on the peripheral smear in patients with DIC, this finding is inconsistent.

The treatment of DIC is more an art than a science because of the paucity of randomized, controlled trials in the medical literature. The primary therapy remains treatment of the underlying disorder. Platelet transfusions should be reserved for the acutely bleeding patient with a platelet count of < 50,000/μL or for prophylaxis when invasive procedures are planned. Although concern exists about worsening DIC by transfusing blood components, there is little evidence from controlled clinical trials that blood components "fuel the fire" in DIC. Therefore, in actively bleeding patients with DIC, 8 units of cryoprecipitate should be infused to replace fibrinogen in patients whose levels are less than 100 mg/dL. Similarly, fresh frozen plasma can be administered to correct a prolonged prothrombin time (e.g., international normalized ratio [INR] > 1.5). The use of heparin can partially reduce the coagulopathy in DIC, and a large trial in patients with severe sepsis suggests a benefit of low-dose heparin on 28-day mortality. The use of tissue factor pathway inhibitors and antithrombin III has not shown survival benefit. Likewise, the survival benefit that was observed in the first clinical trial of activated protein C in patients with DIC and severe sepsis could not be reproduced 10 years later in a second pivotal clinical trial in the same patient population with the resulting withdrawal of that product from the market. Other therapies, such as recombinant factor VIIa, have been used to treat DIC anecdotally, but insufficient data exist to recommend their routine use.

OTHER CAUSES OF THROMBOCYTOPENIA

Several drugs can cause platelet destruction on a nonimmune basis. Two such drugs, cyclosporine and mitomycin C, induce a condition identical to HUS. On an immune basis, quinine-dependent antibodies can induce a HUS-like syndrome. Treatment of drug-induced thrombocytopenia involves discontinuing the offending drug.

Thrombocytopenia can complicate a variety of infections, even in the absence of DIC. Bacterial infections and sepsis syndrome can be associated with platelet aggregation and destruction. Rickettsial infections can cause vasculitis, leading to platelet adhesion and destruction. Malaria commonly presents with thrombocytopenia. These infection-associated thrombocytopenias resolve with treatment of the infection.

Antiphospholipid antibody syndrome can lead to thrombocytopenia on an immune basis. Thrombocytopenia resulting from the mechanical destruction of platelets can occur in aortic valvular dysfunction or with extracorporeal bypass. Treatment involves replacing the dysfunctional valve or allowing platelet counts to recover following extracorporeal bypass.

Disorders of Increased Platelet Destruction by Immune Mechanisms

Although immune (idiopathic) thrombocytopenic purpura (ITP) (see Chapter 63) may on occasion lead to admission to the ICU, ITP is not a common cause of new onset thrombocytopenia in ICU patients. Rather, immune-mediated thrombocytopenia resulting from drugs is the most common cause of thrombocytopenia in the ICU setting (see Box 45.2).

DRUG-INDUCED THROMBOCYTOPENIA

Drug-induced thrombocytopenia in the ICU is common (30% to 50%) and is difficult to differentiate from other causes of thrombocytopenia in critically ill patients. However, it is important to identify and remove any potentially offending drug in the treatment of thrombocytopenia in the ICU. Most drug-induced thrombocytopenia becomes evident about 1 week after initiation of the offending drug. Such is the case with heparin and trimethoprim-sulfamethoxazole. However, some drugs can cause a fall in platelet count in as soon as 1 to 2 days after initiation such as the platelet glycoprotein IIb/IIIa inhibitors tirofiban, eptifibatide, and abciximab. A comprehensive summary of reports of drug-associated thrombocytopenia can be found at http://w3.ouhsc.edu/platelets.

HEPARIN-INDUCED THROMBOTIC THROMBOCYTOPENIA (HITT)

Though heparin-induced thrombotic thrombocytopenia (HITT) affects less than 1% of ICU patients, it can cause significant morbidity and mortality as a result of arterial and venous thrombosis. In a patient previously unexposed to heparin, heparin-associated thrombocytopenia within the first 4 days of exposure is usually mild, transient, and not associated with immune complex formation (often referred to as heparin-induced thrombocytopenia [HIT] type 1). Heparin in these cases can be continued, and spontaneous recovery of platelet count is expected. In contrast, in previously exposed patients, heparin-induced thrombocytopenia (referred to as HIT type 2) associated with immune complex formation can be life and limb threatening. HIT type 2 typically occurs 5 to 14 days following rechallenge with heparin. HIT type 2 is more commonly seen with use of unfractionated heparin than low-molecular-weight heparin and is more frequent in surgical patients, especially after cardiac surgery. Thrombocytopenia is more pronounced in HIT type 2 than HIT type 1 with a platelet count drop of > 50% from baseline. Less commonly, in patients previously exposed to heparin, HIT may occur within hours of reexposure. A common scoring system, the "4Ts" system, has been prospectively validated to predict the likelihood of HIT in thrombocytopenic patients (Table 45.1).

The pathophysiology of thrombocytopenia in HIT involves immune complex formation. These immune complexes form when platelet factor 4 (PF4—a protein contained in platelet alpha granules) binds to heparin. HIT results from antibody (IgG) formation to heparin-PF4 complexes, which, in combination, are able to induce platelet aggregation. After aggregation, the platelets are usually cleared from the circulation, but in about 20% of cases, they also cause venous

TABLE 45.1 ■ **The "4Ts" Prediction System for Heparin-induced Thrombocytopenia (HIT)**

Points (0, 1, 2 for Maximum Score = 8)	**2**	**1**	**0**
Thrombocytopenia	> 50% decrease	30%–50% decrease	< 30% decease
Timing of onset of platelet decrease	Days 5–10	> Day 10	< Day 4
Thrombosis	Proven new thrombosis or skin necrosis	Progressive or recurrent thrombosis	None
Other causes of platelet decrease	None	Possible	Definite

Pretest probability: score 6 to 8 = High, score 4 to 5 = Intermediate, score < 3 = Low.
Adapted from Warkentin TE: Heparin-induced thrombocytopenia: diagnosis and management. Circulation 110:e454-e458, 2004.

or arterial thrombosis. The patient's blood can be assessed for HIT in the laboratory by demonstrating the presence of heparin-PF4 antibodies by enzyme-linked immunosorbent assay or by demonstrating the release of the granule contents of normal platelets on exposure to therapeutic concentrations of heparin in the presence of the patient's plasma.

A high index of suspicion is needed to infer HIT and its more life-threatening related condition, HITT. For example, any arterial clot occurring in a patient receiving heparin in the ICU should be suspected as being caused by HITT that may occur with or without a detectable fall in platelets. This so-called white clot syndrome (reflecting the unusual gross appearance of the clot in occluded arteries) carries high morbidity and up to 28% mortality in one large series. The suspicion for HITT should arise when a patient receiving heparin acquires a venous clot distinct from the one that triggered the heparin therapy. Additionally, a decline of > 50% in the platelet count or a drop in platelet count to less than 100,000/μL also increase the likelihood of HITT. Other warning signs of HITT are the development of heparin resistance, skin necrosis (especially at sites of prior subcutaneous heparin injections), and abdominal or limb pain. The most common sites of arterial thrombosis in HITT are the distal aorta and iliofemoral arteries. Others vessels at risk include native coronary vessels, coronary bypass grafts, and spinal and cerebral arteries. Previously injured vessels—for example, at sites of prior catheter insertions—seem predisposed to HITT clots.

Treatment of HIT and HITT consists of the prompt removal of all sources of heparin and the initiation of alternative means of anticoagulation. Even the smallest amount of heparin, such as the heparin coating of some intravascular catheters, can induce and exacerbate HIT. Even in the absence of thrombosis, thrombocytopenia in HIT should be treated with alternative anticoagulation because of the high risk of thrombosis. Options for anticoagulation include heparinoids (e.g., danaparoid), direct thrombin inhibitors (e.g., lepirudin, argatroban, bivalirudin), and factor Xa inhibitors (e.g., fondaparinux). Importantly, low-molecular-weight heparin should be avoided because it shows cross-reactivity to heparin when tested by heparin-induced antiplatelet antibodies. The use of vitamin K antagonists (e.g., warfarin) is contraindicated until the platelet count has risen to at least above 150,000/μL because of the thrombotic risk imparted by warfarin's ability to decrease levels of protein C and S. After removal of heparin, most platelet counts recover spontaneously in several days. Repeat exposure to heparin in patients with HITT may lead to recurrent arterial clots and death. Platelet transfusions in HIT are contraindicated because the infused platelets may aggregate and cause thrombosis.

POSTTRANSFUSION PURPURA

A rare cause of thrombocytopenia is posttransfusion purpura (PTP). This condition is characterized by severe thrombocytopenia occurring 7 days after a blood transfusion. PTP most commonly occurs in the 10% of patients whose platelets lack the Pl^{A1} antigen, a polymorphism of glycoprotein IIIa. These patients acquire alloantibodies to Pl^{A1}. On exposure to transfused platelets possessing the Pl^{A1} antigen, alloantibodies to Pl^{A1} destroy both transfused platelets and native platelets. Treatment for PTP includes plasmapheresis to remove the offending antibody, circulating antigen, or both. Platelet transfusions are to be avoided in PTP because the transfused platelets are likely to be Pl^{A1}-positive again, and they may cause life-threatening transfusion reactions. Patients with PTP should receive blood only from individuals known to be negative for Pl^{A1}. PTP should be considered in all cases of severe thrombocytopenia that occur 7 days after a blood transfusion.

Disorders of Decreased Platelet Production

Thrombocytopenia, resulting from decreased platelet production, is characterized by a decrease in the number of megakaryocytes in the bone marrow. A major group of acquired diseases that result in platelet hypoproduction in the marrow are infiltrative diseases, such as leukemia,

myelofibrosis, and metastatic tumors. In all of these conditions, the peripheral smear reveals thrombocytopenia with erythrocytes that are teardrop shaped (dacryocytes). In addition, leukoerythroblastosis may be observed, characterized by nucleated red blood cells and early myeloid forms. Definitive diagnosis of these conditions is made by reviewing the bone marrow biopsy and aspirate results.

Aplastic anemia is characterized by a reduction in the marrow production of all cell lines. Amegakaryocytic thrombocytopenia is a variant of aplastic anemia and is characterized by the absence of megakaryocytes, with preservation of other cell lines. Thrombocytopenia is part of both of these disorders.

Viral infections commonly result in decreased platelet production. Mumps, varicella, parvovirus, cytomegalovirus (CMV), Epstein-Barr virus (EBV), HIV, and other conditions are associated with thrombocytopenia that is usually mild. These usually self-limited disorders and the resultant thrombocytopenias require no therapy.

Decreased platelet production is also seen in vitamin B12, folate, and iron deficiency, as well as alcoholism. Finally, a major feature of ITP, in addition to immune destruction, is decreased platelet production.

Hypoproductive thrombocytopenia is usually treated with platelet transfusions when patients are bleeding or if the platelet count is low enough to require prophylactic platelet transfusions. A threshold platelet count for prophylactic transfusions has not been firmly established for all patient populations (Chapter 19) but is generally less than 10,000/μL. Several drugs—including recombinant IL-11 (oprelvekin), romiplostim, and eltrombopag—work to increase platelet production in patients with platelet hypoproduction.

Disorders of Platelet Sequestration

Normally, one third of the body's total numbers of platelets are pooled in the spleen. Platelet sequestration can be exaggerated in liver cirrhosis, portal venous hypertension, or splenomegaly. Splenomegaly can result from cirrhosis, heart failure, lymphoproliferative disorders (e.g., lymphoma), myeloproliferative disorders (e.g., leukemia, polycythemia vera, myelofibrosis), hemoglobinopathies (e.g., hemoglobin C or SC disease, hemoglobin SS in children, thalassemias), Gaucher disease, and various infectious diseases (e.g., CMV, EBV, hepatitis, malaria, babesiosis). All have been associated with thrombocytopenia. In these conditions, platelet production is normal and the total body content of platelets may be normal with an increased fraction of platelets pooled in the spleen. Thrombocytopenia resulting from splenic sequestration usually results in platelet counts > 50,000/μL. Because circulating platelets function normally and platelets can be mobilized from the spleen if needed, splenic sequestration usually requires no therapy. Thrombocytopenia has also been reported transiently in hypothermic patients, presumably from platelets pooling in the spleen. On rewarming, platelet counts usually return to normal.

Platelet Transfusion Therapy

Since the development of plastic tubing in the 1960s, platelets have been available for transfusion. Platelet transfusions are often given to treat the thrombocytopenia associated with the preceding disorders of platelet production (Chapters 19 and 24). A study published in 1997 looked at patients receiving induction chemotherapy for acute myelogenous leukemia and concluded that a platelet count of 10,000/μL (or 10,000 to 20,000/μL when body temperature exceeded 38° C) was as safe as the previously established threshold of 20,000 per cubic millimeter.

The surgical literature maintains that preoperative platelet counts should be at least 50,000/μL for most procedures and at least 100,000/μL for neurologic or ophthalmic procedures. A threshold

TABLE 45.2 ■ **Treatment of Thrombocytopenia in Various Disorders**

Disorder	Treatment
DIC	Treat underlying cause; transfuse platelets only if actively bleeding
Drug-induced	Remove offending drug
Hypothermia	No treatment needed
Hypersplenism	No treatment needed
ITP	Glucocorticoids, intravenous immunoglobulin (IVIG), anti-D immune globulin (Rhogam), rituximab, splenectomy (see Chapter 63)
Production problems	Platelet transfusions if actively bleeding or if platelets < 10,000/μL (see Chapters 19 and 24 for other recommended thresholds for transfusions)
PTP	Plasmapheresis
TTP	Plasmapheresis, +/– glucocorticoids, *avoid* platelet transfusions (see Chapter 63)

DIC, disseminated intravascular coagulation; ITP, immune thrombocytopenic purpura; IVIG, intravenous immunoglobulin; TTP, thrombotic thrombocytopenic purpura; PTP, posttransfusion purpura.

platelet count of 50,000/μL also appears reasonable for most ICU procedures, including insertion of central venous catheters, lumbar puncture, thoracentesis, paracentesis, and other minor surgeries, including incision and drainage and chest tube insertion. The results of a study establishing how many platelets to transfuse in certain disorders of marrow underproduction suggest that a lower dose (1.1×10^{11}) is as effective as a higher transfused dose (4.4×10^{11}) in preventing bleeding.

Clinical Pearls

1. Avoid platelet transfusions in TTP, HUS, HIT, HITT, or PTP unless there is life-threatening hemorrhage.
2. In disorders of platelet production, transfuse platelets prophylactically if the platelet count is less than 10,000/μL. If an invasive procedure is planned, platelet counts should be at least 50,000/μL.
3. If a patient becomes thrombocytopenic in the ICU, first think about drugs such as heparin.
4. Remember that HIT, though associated with thrombocytopenia, can also cause arterial or venous thrombosis.
5. In many disorders causing thrombocytopenia (Table 45.2), one must treat the underlying cause and not simply transfuse platelets.
6. Review of the peripheral smear can provide clues to the pathogenesis of thrombocytopenia and should be the first step in the approach of any thrombocytopenic patient (Figure 45.2).

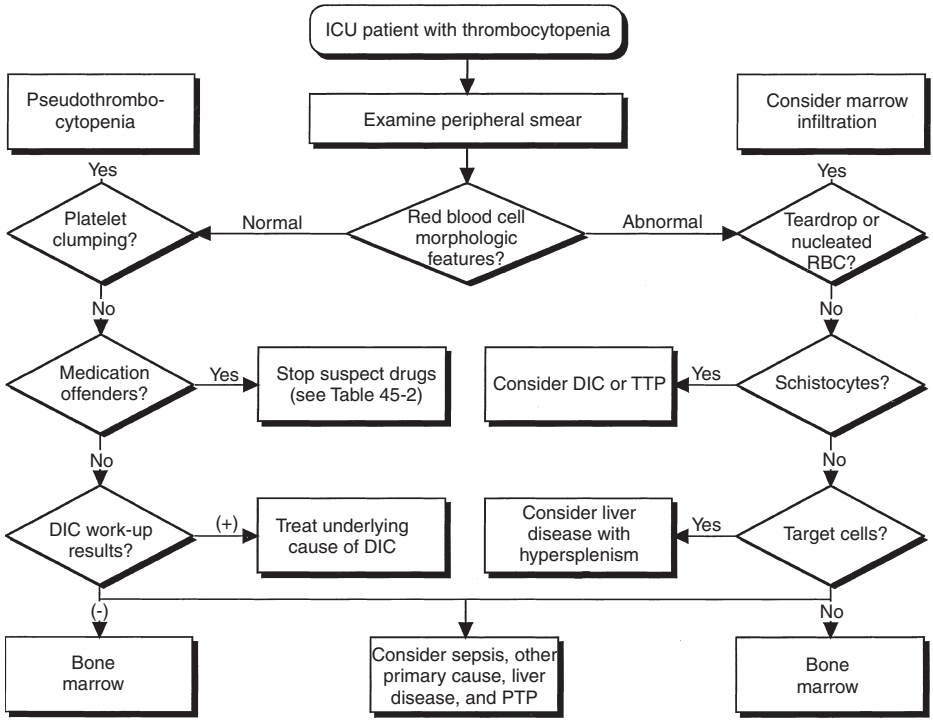


Figure 45.2 Schematic flow diagram outlining the diagnostic evaluation of an ICU patient who acquires or presents with thrombocytopenia. DIC workup includes measurement of fibrinogen, fibrin degradation products, and prothrombin and partial thromboplastin times. RBC, red blood cell; DIC, disseminated intravascular coagulation; TTP, thrombotic thrombocytopenic purpura; PTP, posttransfusion purpura.

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CHAPTER 46

Transfusion Reactions

Una O'Doherty Siegel ■ Don L. Siegel

A transfusion reaction can be defined as any unexpected patient sign or symptom during or following the transfusion of a blood product. Transfusion reactions may be acute or delayed, immune or nonimmune mediated, and clinically insignificant or potentially life threatening. Mild reactions include allergic and febrile reactions that occur with ~1% of transfusions. Potentially fatal reactions are rare and include transfusion-related acute lung injury (TRALI), acute hemolytic transfusion reactions (AHTRs), septic reactions, and anaphylaxis.

Both mild and serious transfusion reactions can occur even when procedures are followed appropriately. Such reactions to blood products occur with a predictable frequency (Table 46.1). Additional laboratory testing by the blood bank is often required to determine the etiology of the suspected transfusion reaction, the specifics of which take into account the type of blood product transfused. For example, TRALI can occur with any plasma-containing product (fresh frozen plasma [FFP], units of packed red blood cells [RBCs], and platelet concentrates), whereas AHTRs occur most frequently with RBC products.

In the context of transfusion reactions, this chapter only considers those that are acute. Indications for transfusions are discussed elsewhere (see Chapter 19). Also discussed elsewhere are acute reactions of particular concern with massive transfusion, including hypocalcemia and other electrolyte and metabolic disorders (see Chapter 39) and hypothermia (see Chapter 55).

Definitions and Pathophysiologic Mechanisms

TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)

TRALI is now considered to be the most common cause of fatal transfusion reactions. Approximately 43% of transfusion fatalities reported to the Food and Drug Administration (FDA) are attributed to TRALI. The precise pathophysiology of TRALI remains debated and appears to be multifactorial. Classically TRALI has been thought to occur when antibodies in donor plasma bind to recipient granulocytes via human leukocyte antigens (HLAs) or granulocyte-specific alloantigens, and then activate the granulocytes causing degranulation within the lung vasculature. The degranulation in turn triggers acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS). However, cases of TRALI based on clinical and radiographic findings have occurred in the absence of demonstrable anti-granulocyte antibodies. Thus, the exact mechanisms that lead to TRALI remain incompletely understood.

ACUTE HEMOLYTIC TRANSFUSION REACTIONS (AHTR)

Approximately 23% of transfusion fatalities reported to the FDA are due to acute hemolysis of RBCs (i.e., AHTRs). AHTRs occur when antibodies against RBC antigens strongly fix complement and produce brisk intravascular hemolysis. The activation of complement triggers

TABLE 46.1 ■ **Frequencies of Acute Transfusion Reactions**

Type of Reaction	Estimated Frequency (per Transfused Unit)
Mild allergic reaction	1/33–1/100
Febrile transfusion reaction	1/100–1/200
Volume overload	1/100–10,000
Transfusion-related acute lung injury (TRALI)	1/5000‡
Acute hemolytic transfusion reaction (symptomatic)	1/12,000–1/33,000
Anaphylactic reaction	1/20,000–1/50,000
Septic reaction	1/50,000*
Nonimmune hemolysis	Unknown†

*Apheresis platelet units that have been tested for bacteria by culture.
†Although the actual incidence of nonimmune hemolysis is not well documented, it appears to be rare.
‡Milder forms may not be rare but are likely to go unrecognized.

the coagulation cascade and elevated bradykinin. Brisk hemolysis also leads to the formation of RBC membrane fragments (stroma) and tissue factor. Together, these responses can lead to hypotension, renal failure, disseminated intravascular coagulation (DIC), and bleeding. Hypotension occurs from elevated bradykinin and tumor necrosis factor alpha (TNF-α). Renal failure may occur because of reactive renal splanchnic vasoconstriction after bradykinin release and acute renal tubular necrosis from toxicity of the RBC stroma. Historically it was thought that AHTRs resulted from clerical errors leading to the transfusion and subsequent destruction of ABO-incompatible blood by recipient IgM anti-carbohydrate antibodies. However, FDA data indicate that fatal AHTRs can also be caused by certain complement-fixing *IgG* antibodies directed against protein antigens on the RBC surface, such as those in the Kidd blood group system.

FEBRILE TRANSFUSION REACTIONS

Transfusion of blood products that contain leukocytes, such as platelets and less frequently RBCs, can be associated with an isolated rise in body temperature as the apoptotic white blood cells (WBCs) release cytokines. Cytokine release may be enhanced when the recipient contains anti-leukocyte antibodies that cross-link the transfused WBCs (leukoagglutinins). These reactions are classified as febrile nonhemolytic transfusion reactions when other causes of fever have been ruled out. Febrile reactions occur in ~1% of transfusions in which the transfused blood products have not undergone either prestorage or bedside leukoreduction filtration. The incidence of febrile nonhemolytic transfusion reactions have been reduced in frequency because of the adoption of "universal leukoreduction" programs by many blood collection centers.

ALLERGIC AND ANAPHYLACTIC REACTIONS

Allergic reactions occur in 1% to 3% of transfusions. Anaphylaxis occurs with 1 in 20,000-50,000 transfusions. These reactions occur when antibodies exist against soluble plasma proteins introduced by any plasma-containing blood product. The actual protein antigen that causes the reaction is generally not identified and this type of reaction is often idiosyncratic, specific to a particular donor/recipient pair who are unlikely to cross paths again. The one notable exception is when plasma containing IgA antibodies serves as the allergen, upon transfusion into an IgA-deficient patient. In the most severe cases, anaphylaxis can occur when the recipient has high titer

IgE antibodies against IgA. Fortunately, most IgA-deficient recipients are incompletely deficient in IgA and thus are not at risk for anaphylaxis. Mild reactions are generally limited to urticaria.

Septic Reactions

Approximately 5% of fatal transfusion reactions are due to bacterial contamination of blood products. Platelet products are most often implicated because they are stored at room temperature (red cells are stored refrigerated and FFP is stored frozen). The incidence of fatal transfusion reactions resulting from bacterial contamination reported to the FDA has decreased since implementation of bacterial culturing of apheresis platelet products.

Bacteria can contaminate blood products because of their presence on skin plugs or from transient bacteremia in blood donors. Among platelet products, pooled platelet products derived from whole blood donations (versus apheresis collection) have the highest contamination rate because they come from four to six donors. Though most common gram-positive bacteria cause septic transfusion reactions, products contaminated with gram-negative bacteria can cause the most serious reactions partly because of endotoxin. RBC products rarely cause sepsis, but when occurring, bacteria such as *Yersinia enterocolitica,* which grow well in the cold, may be responsible.

The parasite *Babesia microti* has been identified as the most frequent cause of transfusion transmitted microbial infection that led to death in 2007-2011. These infections do not cause acute transfusion reactions as generally it takes ~2-10 weeks for the parasite to replicate to significant levels for symptoms to appear.

NONIMMUNE HEMOLYTIC REACTIONS

Nonimmune hemolysis causes less than 3% of fatal transfusion reactions that are reported to the FDA. Nonimmune hemolysis occurs when RBCs are mixed with nonisotonic intravenous (IV) solutions; exposed to extreme temperatures, such as transfusion through malfunctioning blood warmers; or transfused too rapidly, particularly through needles that are too narrow in gauge.

VOLUME OVERLOAD REACTIONS

Volume overload, the most common nonimmune-mediated transfusion reaction, occurs in less than 1% of transfusions. Volume overload causes ~15 % of transfusion-related fatalities that are reported to the FDA. Transfusion often leads to hypervolemia given the large volume of blood products.

Differential Diagnosis

If the vital signs of a patient change or if symptoms such as hives or shortness of breath develop during a transfusion, one should stop the transfusion and evaluate the patient for a transfusion reaction. However, the signs and symptoms of transfusion reactions are nonspecific (Table 46.2). For example, fever can be the only symptom in an innocuous febrile reaction, or it can herald an acute hemolytic reaction. Thus, all potential transfusion reactions require investigation and diagnoses guided by the type of blood product transfused (Table 46.3). For example, the appearance of hives during a transfusion of FFP likely reflects an allergic reaction, whereas the acute onset of a body temperature of 104° F following the transfusion of a whole blood–derived pooled platelet product raises suspicion of a septic transfusion reaction.

The four most serious transfusion reactions of TRALI, AHTR, sepsis, and anaphylaxis are all associated with hypotension. TRALI is diagnosed by detecting bilateral lung infiltrates in the absence of congestive heart failure (CHF). Though the measurement of brain natriuretic peptide (BNP) was suggested to distinguish cardiogenic (hemodynamic) pulmonary edema from

TABLE 46.2 ■ **Symptoms and Signs of Acute Transfusion Reactions**

Type of Reaction	Anxiety	Chills/ Rigors	Dyspnea	Flank Pain	Hives	Fever	Tachycardia	Hypotension
Acute hemolytic transfusion reaction*	+++	++	++	+++	–	++	++	+++
Febrile transfusion reaction	+	++	–	–	–	++	+	–
Mild allergic reaction	+	–	–	–	+++	–	–	–
Anaphylactic reaction	++	–	++	–	+	+	++	+++
Septic reaction	+	++	++	–	–	+++	++	+++
Nonimmune hemolysis	–	–	–	–	–	–	–	–
Volume overload	+	–	++	–	–	–	+	–
Transfusion-related acute lung injury (TRALI)	+	+++	+++	–	–	++	+	+++

*Acute hemolytic transfusion reactions may also cause nausea, flushing, dyspnea, oliguria, and generalized bleeding.
Scoring scale: –, not present; +, mild sign or symptom; ++, moderate sign or symptom; +++, severe sign or symptom.

TABLE 46.3 ■ **Transfusion Products Associated with Various Types of Acute Transfusion Reactions**

Type of Reaction	Products Commonly Implicated	Products Rarely Implicated
Acute hemolytic transfusion reaction	RBCs	Platelets, FFP
Febrile transfusion reaction	Platelets, RBCs	FFP
Mild allergic reaction	RBCs, platelets, FFP	—
Anaphylactic reaction	RBCs, platelets, FFP	—
Septic reaction	Platelets (RBCs on occasion)	FFP
Nonimmune hemolysis	RBCs	—
Volume overload	RBCs, FFP	Platelets
Transfusion-related acute lung injury (TRALI)	RBCs, platelets, FFP	—

RBCs, red blood cells; FFP, fresh frozen plasma.

TRALI, the discriminatory value of BNP is unreliable because of the overlap of "normal" and elevated levels. Also, as often as 50% of the time, the onset of symptoms during a transfusion is due to the recipient's underlying disease and coincidental to the transfusion.

Diagnostic Evaluation

Signs and symptoms of transfusion reactions can be quite variable from patient to patient. For example, most septic reactions result in high fevers. However, concomitant treatment with

BOX 46.1 ■ Stepwise Clinical Management of Suspected Transfusion Reaction

If a transfusion reaction is suspected, take the following steps:

1. Stop the transfusion and maintain intravenous (IV) access to facilitate fluid support if necessary.
2. Check the identifiers on the patient's wristband and on the blood product to rule out potential clerical error (i.e., misidentification of a patient who was the recipient with the anticipated recipient of the blood product).
3. Notify the blood bank (transfusion service) of the event (particularly important as another patient in the institution could be at risk because of a mixup in specimen identification).
3. Return the entire transfusion set, blood product bag, and residual untransfused product to the blood bank, along with a set of post-transfusion blood specimens required by the institution's protocol (e.g., anticoagulated or serum tubes of blood or both).
4. Send additional patient specimens to appropriate laboratories depending on the nature of the suspected transfusion reaction and the necessary diagnostic tests to be performed (Table 46.4).

high-dose corticosteroids may blunt fever. Hypotension is variable in sepsis. AHTR symptoms can initially be very mild but then rapidly progress to renal failure, shock, and death. For this reason, it is imperative to investigate every untoward reaction during transfusion (Box 46.1).

Note that in two scenarios, it may be reasonable to continue a transfusion in the setting of a suspected reaction. First, if the symptoms are limited to urticaria and the urticaria resolves with an antihistamine (histamine type 2 receptor antagonist), such as diphenhydramine, then it is generally acceptable to restart the transfusion once the urticaria has resolved. In the second scenario, if the symptoms are limited to fever and the clinical team caring for the patient deems the fever related to the patient's underlying disease and coincidental with the timing of the transfusion, then it may be possible to restart the transfusion if permitted by institutional transfusion policy. However, one should not restart a transfusion if the transfusion set has been disconnected or if the mandated transfusion completion time has elapsed (e.g., 4 hours for packed RBCs).

Management and Discussion of Therapies

The first few steps in managing a transfusion reaction were outlined earlier. General supportive care is the rule (e.g., place patients in circulatory shock in the Trendelenburg position and administer IV fluids, supplemental oxygen, and other standard intensive care unit [ICU] supportive care). Hypotension unresponsive to IV fluids requires vasopressors (see Chapter 10). Treatment of anaphylaxis includes epinephrine (see Chapter 32), such as 0.2 to 0.5 mL of subcutaneous (SQ) or intramuscular (IM) injection of epinephrine (1:1000) given subcutaneously or via parenteral route. Treatment of suspected sepsis includes early administration of empiric broad-spectrum antibiotics to cover gram-negative and gram-positive organisms (see Chapter 19).

In cases of TRALI, supportive care includes giving supplemental oxygen and, in severe cases, non-invasive or invasive ventilatory support while excluding other causes of acute respiratory distress. In AHTR, one should monitor urine output and renal function, and promote diuresis with IV fluids. Although lacking strong evidence, some clinicians would give diuretics (e.g., 40-80 mg furosemide IV) in nonhypovolemic adults. In a similar manner, one should treat hypotension and renal failure from nonimmune hemolysis. Administration of diuretics is indicated for volume overload. Mild urticaria generally responds to an antihistamine (e.g., 25 to 50 mg IV diphenhydramine). In recurrent allergic reactions, premedication with 50 mg IV diphenhydramine and 300 mg oral ranitidine may prevent mild reactions and avoid potential wastage of blood products. The addition of 50 mg oral prednisone as prophylaxis can help more severe moderate allergic reactions. For IgA-deficient patients with true allergy to IgA, blood products collected from IgA-deficient donors are indicated. This requires planning and coordination with the institution's local blood collection center.

TABLE 46.4 ■ **Laboratory Findings Associated with Acute Transfusion Reactions**

Type of Reaction	Direct Anti-Globulin Test*	Visible Hemolysis*	Hemoglobin-uria*	Gram Stain Of Blood Product	Culture of Blood Product	Bilirubin, Lactic Dehydrogenase	BNP Brain Natriuretic Peptide
Acute hemolytic transfusion reaction	+	+	+	–	–	Increased	–
Febrile transfusion reaction	–	–	–	–	–	–	–
Mild allergic reaction	–	–	–	–	–	–	–
Anaphylactic reaction	–	–	–	–	–	–	–
Septic reaction	–	–	–	May be positive	+	–	–
Nonimmune hemolysis	–	+	+	–	–	May be increased	–
Volume overload	–	–	–	–	–	–	+
Transfusion-related acute lung injury (TRALI)	–	–	–	–	–	–	–

*This assumes that these tests were negative before transfusion. Otherwise, an increase in the strength of the direct antiglobulin test or the amount of hemolysis or hemoglobinuria may be observed. Traditionally this has been termed a *direct Coombs test*, which tests for the presence of immunoglobulin directed against donor RBC.

PREVENTION OF TRANSFUSION REACTIONS

Clerical errors—either the mislabeling of blood samples or the mistransfusion of a blood product intended for a different patient—can lead to the most serious types of transfusion reactions (i.e., AHTRs). Therefore, it is absolutely essential to label all blood specimens at the bedside and strictly follow proper patient identification procedures when administering blood products.

Approaches to avoid the other serious, nonhemolytic transfusion reactions are generally beyond the control of those who actually order and transfuse blood. For example, TRALI may be associated with the presence of donor anti-HLA antibodies; and the majority of donor anti-HLA antibodies originate in multiparous women. On this basis, some blood collection centers limit production of plasma products only to male donors. The requirement for bacterial culturing of apheresis platelet products by collection centers has reduced the frequency of contaminated units by more than half. As noted earlier, the incidence of nonhemolytic febrile reactions has been significantly reduced by the leukoreduction filtration of blood products at the time of collection or at the bedside.

Clinical Pearls and Pitfalls

1. When discussing transfusion risks with patients, clinicians should appreciate that patients are often most concerned about the risks of acquiring an infectious disease through transfusion. For example, the per unit risk of contracting HIV or hepatitis C is estimated at 1 in 3 million. Yet the risk of death from an acute intravascular ABO-mediated hemolytic transfusion reaction (AHTR) resulting from an easily avoidable clerical error is about 6 to 15 times greater (~1:200,000 to 1:500,000 units transfused). With these statistics in mind, the importance of minimizing medical errors by the proper labeling of blood tubes and of patient identification cannot be overemphasized (see Chapter 107).
2. ICU clinicians should investigate all transfusion reactions and strictly follow institutional policies for the workup of suspected reactions. During the laboratory investigation of a reaction, the institution's transfusion service typically holds all routine releases of blood products. The hold allows sufficient time to verify the patient's blood type and ensure all required blood samples are drawn before introducing an additional donor blood component. If a patient needs blood during this critical period of time (while the hold is ongoing), ICU clinicians should directly contact the blood bank medical director to ensure that potentially lifesaving blood products are not withheld to the potential detriment of the patient. Every transfusion service is required to have a blood bank physician available to discuss the investigation and management of transfusion reactions.

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CHAPTER 47

Ventilator Alarm Situations

Michael J. Frazer ■ Paul N. Lanken

Contemporary microprocessor-based mechanical ventilators provide a wide selection of ventilatory modes that can customize assisted and spontaneous ventilation to individual patients (Chapter 2). These technologically advanced ventilators also incorporate a variety of alarms to alert intensive care unit (ICU) clinicians to numerous potentially dangerous situations. Ventilator alarms are designed to inform, but not dictate, the actions necessary to correct the potential hazard. For this reason, it is imperative that ICU clinicians be familiar with the function of the array of these alarms, how to evaluate ventilator alarm situations, and how to successfully manage those situations (Figure 47.1).

Types of Ventilator Alarms

The types and number of alarms that are functional on a ventilator vary depending on which ventilatory mode is being used. In addition, identical alarms may have different meanings and response times in different modes. Finally, alarms can signify different levels of clinical urgency (Table 47.1).

In face of this complexity, the ability to categorize ventilator alarms is essential. All alarms can be categorized into three types based on whether they indicate (1) a ventilator failure, (2) a patient-ventilator interface problem, or (3) a patient-related event.

Because most modern ventilators function by combining a microprocessor-based electromechanical system with a pneumatic system, *ventilator failure* can result from a malfunction in its electronic or pneumatic systems. Ventilator manufacturers incorporate *preset alarms* to ensure the safety of these systems. In the case of a true ventilator failure and not user error—for example, a power cord being disconnected—there is little choice but to recognize the problem quickly and replace the ventilator if necessary.

Patient-ventilator interface problems refer to the interaction of the ventilated patient with the ventilator. Thresholds for alarms arising from problems at this interface are usually set by a respiratory care practitioner and relate closely to the ventilator's monitoring capabilities. Significantly, these alarms may alert the ICU clinician to problems in how ventilatory support is being provided to the patient. They can signify a range of situations, for example, from a patient becoming disconnected from the ventilator to the peak inspiratory flow failing to meet a patient's inspiratory demand. Practitioner settings that are specifically designed to assist in alleviating patient-interface issues include peak inspiratory flow, inspiratory time ("I time") or rise time, and expiratory sensitivity.

Patient-related event alarms are synonymous with "monitoring alarms." They are designed to detect changes in the patient's underlying physiologic condition. When a simple physiologic monitor alarm (e.g., an electrocardiographic [ECG] monitor) activates, the reason for the alarm arises from a patient-related event and not the functioning of the monitor itself. In contrast, a ventilator with its alarms serves not only as a physiologic monitor but also as a therapeutic intervention whose effects are continuously self-monitored. ICU clinicians often have difficulty recognizing when a problem arises from the patient or from the ventilator and distinguishing

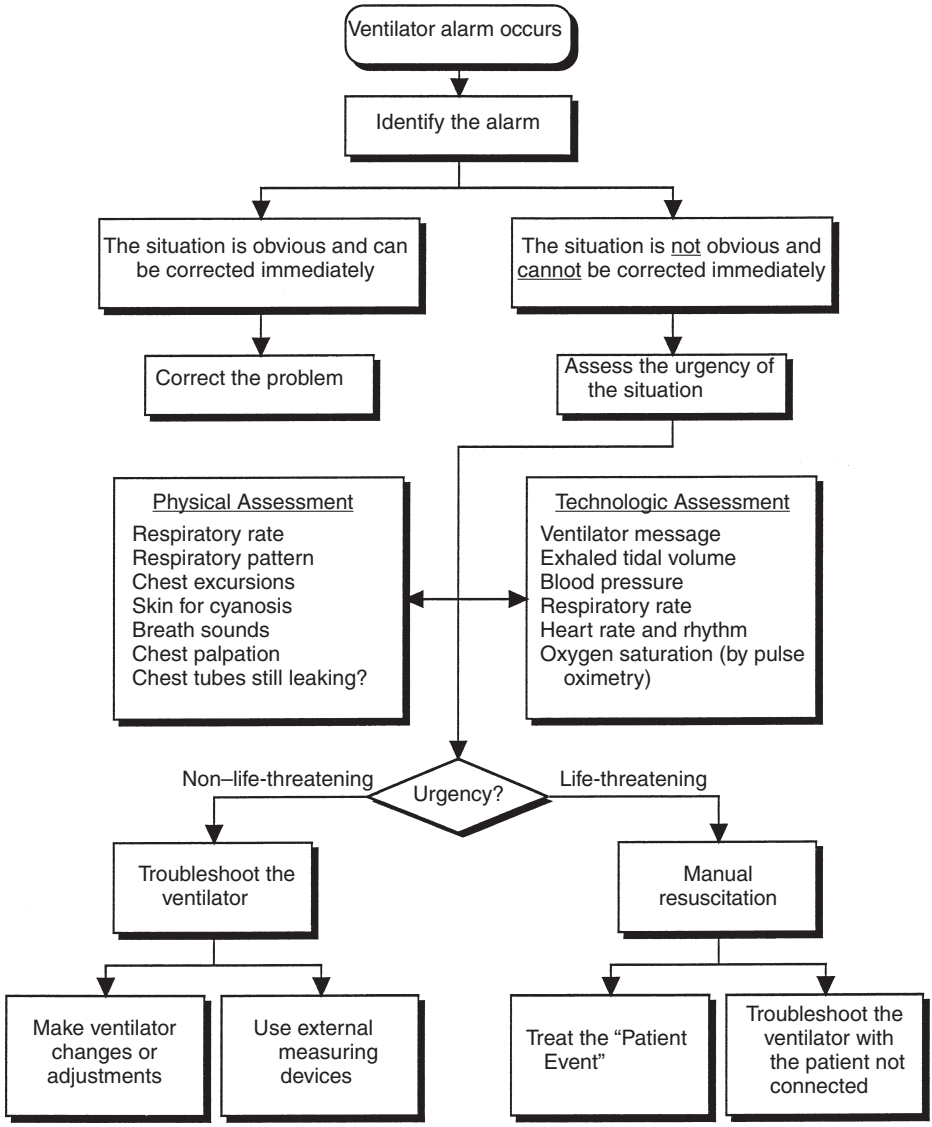


Figure 47.1 Schematic flow diagram of the response to a ventilator alarm.

patient-ventilator interface problems from those solely attributable to the patient (patient-related events).

Each commonly used ventilator alarm is designed to detect a certain acute abnormality, as indicated by its name. Many alarms, however, overlap in the underlying conditions that they detect, as well as in the clinical consequences that they aim to prevent (Table 47.2). For example, if the patient becomes disconnected from the ventilator, multiple alarms activate. Early-response alarms monitor low inspiratory pressure, low exhaled tidal volume, and low positive end-expiratory pressure (PEEP) (if PEEP had been applied before the disconnection). Later alarms include low expired minute ventilation and apnea. Not only do these ventilator-associated alarms form

TABLE 47.1 ■ **Level of Urgency of Ventilator Alarms**

Level*	Priority	Type of Event	Examples
1	Highest	Immediately life threatening	Electrical power failure
			Loss of pneumatic power
			Exhalation valve failure
2	High	Eventually life threatening if problem persists	High airway pressure
			High inspired tidal volume
			Low exhaled minute volume
			Low exhaled volume
			Inverse inspiratory-to-expiratory time (I:E) ratio
3	Low	Not life threatening, or a one-time event	Short period of high respiratory rate
			One-time high airway pressure

*Level is indicated by tone, pitch, or volume of the audio alarm, or by information on the ventilator's visual display, or both.

TABLE 47.2 ■ **Common Ventilator Alarms**

Name of Alarm	Detects	Designed to Prevent
High inspiratory pressure limit	Acute increase in peak airway pressure	Barotrauma
Low inspiratory pressure	Large air leak	Delivery of inadequate tidal volume
	Patient disconnection from ventilator circuit	Hypoventilation, hypoxemia
	Insufficient response by the ventilator to the patient's inspiratory demand	Patient discomfort
		Excessive work of breathing
Low PEEP or CPAP pressure	Small leak in the system	Loss of end-expiratory pressure
		Decrease in Pa_{O_2}
High end-expiratory pressure	Resistance to exhalation	Partial or complete obstruction of expiratory breathing circuit
Low exhaled tidal volume	Air leak	Insufficient ventilatory support
Low inspired tidal volume	Decrease in spontaneous tidal volumes	Hypoventilation
High exhaled tidal volume	Improving lung compliance	Volutrauma, barotrauma, alveolar hyperinflation, and ventilator-associated lung injury (VALI)
High inspired tidal volume	Increased inspiratory demand	
Low respiratory rate	Oversedation	
Low exhaled minute ventilation	Diminished respiratory drive	Patient/ventilator asynchrony
	Decrease in mechanical or spontaneous volumes	Apnea, hypercapnia Insufficient ventilatory support
	Decreased lung compliance*	Hypoventilation
	Onset of respiratory muscle fatigue*	Respiratory compromise
High exhaled minute ventilation	Increase in lung compliance*	Hyperventilation
	Excessive ventilation	Dynamic hyperinflation†
		Acute respiratory alkalosis

Continued on following page

TABLE 47.2 ■ **Common Ventilator Alarms** (Continued)

Name of Alarm	Detects	Designed to Prevent
High respiratory rate	Respiratory distress, including anxiety, pain	Respiratory compromise
		Dynamic hyperinflation†
	Self-cycling ventilator	Patient discomfort
	Onset of respiratory muscle fatigue	Hyperventilation
		Acute respiratory alkalosis
Inverted inspiratory-to-expiratory ratio (I:E)	Self-cycling ventilator	Hyperventilation
	Insufficient expiratory time	Dynamic hyperinflation†
	Inadvertent inspiratory pause	
Apnea	Respiratory arrest	Hypoventilation with hypercapnia
		Hypoxemia
Low oxygen-air inlet pressure	Disconnection of oxygen or compressed air source	Hypoxemia
	Fall in oxygen or air pressure to less than minimal level	Insufficient pressure to power the ventilator's pneumatic system
Power disconnect	Electrical power failure	Failure of all components of the ventilator that require electrical power to operate
	Ventilator unplugged by mistake	
Low or high F_{IO_2}	A variance between the set F_{IO_2} and the analyzed F_{IO_2}	Hypoxemia
		Oxygen toxicity
		Misinformed clinical decisions based on incorrect F_{IO_2}
Ventilator inoperative	Malfunction in the ventilator serious enough to be unsafe for patient use	All potentially harmful effects of the ventilator on the patient
		Insufficient ventilatory support

*Pertains to pressure control and pressure support modes of ventilation.
†Dynamic hyperinflation results in air trapping and auto-PEEP.
PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure.

a redundant safety net, but they also are complemented by nonventilator alarms, such as a pulse oximeter, or ECG lead monitoring. Tables 47.3 to 47.7 list conditions in which alarming is used frequently, with their differential diagnoses, categorized according to site of the problem, and matched with appropriate corrections.

Ventilator Alarms: Identifying the Site of the Problem

Certain alarms fall into both patient-ventilator interface alarms and patient-event alarms categories. Alarms for airway pressures, respiratory rate, and exhaled volumes can have different meanings in different applications and, for this reason, serve as useful examples to consider in detail.

HIGH AND LOW AIRWAY PRESSURE ALARMS

Peak airway pressure, also called peak inflation pressure or peak inspiratory pressure (PIP), is the maximal airway pressure used to deliver a certain tidal volume to the patient. High PIPs result when circuit or airway resistance increases, when lung compliance decreases, or when both occur. Thus, if PIP increases without a decrease in compliance, airway resistance has increased. *High peak pressure alarms* are commonly caused by problems with a patient's airway, such as partial

TABLE 47.3 ■ **Ventilator Alarm Conditions: High Peak Airway Pressures Caused by High Airway Resistance**

Problem	Site of Event	Corrective Action
Coughing	Patient	Suction; increase sedation
Airway occlusion caused by mucous plugs	Patient	Suction; bronchoscopy; give intratracheal *N*-acetylcysteine
Biting on endotracheal tube	Patient	Suction to confirm obstruction at mouth level; insert a bite block
Bronchospasm	Patient	Treat bronchospasm
Patient asynchrony with ventilator	Patient-ventilator interface	Adjust settings to better meet patient needs; reassure anxious patient
Ventilator circuit obstructed by condensed water	Ventilator	Drain water from circuit

TABLE 47.4 ■ **Ventilator Alarm Conditions: High Peak Airway Pressures Caused by Low Respiratory System Compliance**

Problem	Site of Event	Corrective Action
Tension pneumothorax	Patient	Decompress acutely with needle, insert chest tube (Chapter 35)
"Flash" pulmonary edema	Patient	Treat cardiac cause (e.g., ischemia)
Endotracheal tube tip in right main bronchus	Patient-ventilator interface	Confirm with auscultation, reposition ETT and secure
Inverse I:E ratio	Patient-ventilator interface	Shorten inspiration; extend expiration
"Bucking" (resisting positive pressure breath)	Patient-ventilator interface	Sedation, change to more compatible mode; reassure patient
Excessively large tidal volume delivered	Patient-ventilator interface	Decrease tidal volume delivered

I:E, inspiratory-to-expiratory ratio; ETT, endotracheal tube.

obstruction of an endotracheal tube caused by biting, kinking, increased secretions, or bronchospasm (Tables 47.3 and 47.4).

Low airway pressure alarms (Table 47.5) are often associated with air leaks in the ventilator's breathing circuits (e.g., around the cuff of an endotracheal tube) or when the patient's inspiratory effort persists during the inspiration cycle (resulting from enhanced respiratory efforts). In the latter case, the negative pressure that the patient generates during inspiration reduces the peak pressure to less than the threshold set for the low airway pressure alarm.

HIGH AND LOW RESPIRATORY RATE ALARMS

An increase in respiratory rate is one of the first signs that the patient may be experiencing difficulties in breathing. If the ventilator is not providing adequate support—for example, because of a leak in the circuit or a mechanical malfunction—the patient's respiratory rate increases to compensate for insufficient ventilatory support. Patient-related reasons for activation of a *high respiratory rate alarm* include anxiety, pain, an acute neurologic event (resulting in

central neurogenic hyperventilation), hypoxemia, hypercapnia, metabolic acidosis, respiratory distress, and respiratory muscle fatigue or weakness (Table 47.6).

A *low respiratory rate alarm* activates when a patient becomes apneic or the patient's respiratory drive has been acutely suppressed because of sedation (or other causes of central nervous system depression).

LOW EXHALED VOLUME ALARM

A ventilator's breathing circuit and an endotracheal tube provide the means for the ventilator to deliver a volume of gas to the patient's lungs. It is imperative that this be a sealed system to ensure that the patient actually receives the gas volume generated by the ventilator. If there is a leak in this system, the patient receives a smaller than desired tidal volume; this, in turn, results in activation of the *low exhaled volume alarm*. Unless the patient is spontaneously breathing (as noted earlier in the discussion of low peak pressure alarms), most low exhaled volume alarms can be attributed to a leak in the circuit or a leak around the endotracheal (or tracheostomy) tube cuff (Table 47.7). (See Chapters 22 and 30 for more details related to tracheal tubes and their cuffs.) As a rule, ventilators are accurate in delivering volumes to the patient equal to their set tidal

TABLE 47.5 ■ **Ventilator Alarm Conditions: Low Inspiratory Pressure, Low Continuous Positive Airway Pressure, or Low Positive End-Expiratory Pressure**

Problem	Site of Event	Corrective Action
Leak in system	Patient-ventilator interface	Find and correct leak
Leak in system	Ventilator	Pull for service
Faulty exhalation valve	Ventilator	Correct malfunction
Patient disconnection	Patient	Evaluate and reconnect patient
Insufficient peak flow rate	Patient-ventilator interface	Increase flow to meet the inspiratory demand
Ventilator not properly sensing patient's inspiratory effort	Patient-ventilator interface	Adjust ventilator settings to synchronize with patient's efforts
Asynchrony	Patient-ventilator interface	Adjust inspiratory flow rates and sensitivity

TABLE 47.6 ■ **Ventilator Alarm Conditions: High Respiratory Rate**

Problem	Site of Event	Corrective Action
Hypoxia	Patient-ventilator interface	Increase F_{IO_2}
Anxiety	Patient	Increase sedation
Pain	Patient	Increase analgesia
Respiratory muscle fatigue	Patient-ventilator interface	Increase ventilatory support
Dyspnea	Patient-ventilator interface	Increase ventilatory support, treat symptoms with opioids
Low ventilator sensing threshold	Patient-ventilator interface	Adjust sensitivity
Cardiac pulsations	Patient-ventilator interface	Adjust sensitivity
Central neurogenic hyperventilation	Patient-ventilator interface	Give opioids; paralyze patient as last resort

volumes (including automatically taking into account the "lost" tidal volume caused by distension of the circuit during inspiration).

A number of patient-related events can trigger a low exhaled volume alarm. This commonly occurs when the patient's spontaneous tidal volumes decrease, often in conjunction with an increase in the patient's respiratory rate, and is referred to as "rapid shallow breathing." This often signifies the onset of respiratory muscle fatigue. When using pressure control or pressure support modes of ventilation, low (or high) changes in exhaled tidal volume (without a leak in the mechanical system) are a good reflection of changes in respiratory system compliance. In response, the ICU clinician should make ventilator changes to prevent hypoventilation, hyperventilation, or overdistention of the lung. One should keep in mind that if a patient has one or more chest tubes in place that have air leaks, the measured exhaled volume will always be less than the delivered tidal volume because of these air leaks.

HIGH INSPIRED AND EXHALED TIDAL VOLUME ALARMS

Complications such as hyperinflation, nonuniform ventilation, volutrauma, barotrauma, and further damage to lung tissue can happen as a result of high tidal volume ventilation.

Providing "low stretch" low tidal volume ventilation is essential to providing safe ventilation for patients in the ICU setting, especially those with acute respiratory distress syndrome (ARDS) or acute lung injury (ALI) and likewise, most intensivists believe, those at risk for developing ALI or ARDS (see Chapters 2 and 73). Tidal volumes > 8 mL/kg/predicted (lean) body weight (PBW) are believed to be associated with increasing lung inflammation and injury in patients with ARDS and ALI, leading to an increase in morbidity/mortality.

The *high exhaled tidal volume alarm* audibly and visually notifies the practitioner that tidal volumes have exceeded the desired range. This alarm is active in both spontaneous and mandatory volume and pressure modes of ventilation.

The *high inspired tidal volume alarm limit* will also audibly and visually notify the practitioner and, importantly, terminate the breath at the alarm setting ensuring the patient does not receive

TABLE 47.7 ■ **Ventilator Alarm Conditions: Low Exhaled Tidal Volume**

Problem	Site of Event	Corrective Action
Rapid shallow breathing	Patient or patient-ventilator interface	Adjust ventilator settings
Leak in circuit	Patient-ventilator interface	Correct leak
Patient disconnected	Patient-ventilator interface	Reconnect patient
Leak through chest tube	Patient	Adjust alarms
Patient's spontaneous tidal volume decreased	Patient	Adjust ventilatory support
Decreased lung compliance (in PS)	Patient	Evaluate patient
Alarm set improperly	Patient-ventilator interface	Adjust alarms
Leak around tracheal cuff	Patient-ventilator interface	Evaluate, reposition, and reinflate tracheal cuff using a cuff pressure manometer. If cuff pressure to seal leak exceeds 25 mm Hg, consider changing tube (Chapter 22)

PS, pressure support mode of ventilation.

further volume. This alarm is active in alternative spontaneous and mandatory pressure modes of ventilation (see Table 47.2).

The practitioner should monitor patients closely during their ventilatory course to ensure tidal volumes do not exceed the desired range. Reasons for high tidal volumes vary. During volume-cycled ventilation modes (Chapters 2 and 73), tidal volumes are set by the practitioner. Setting a tidal volume larger than 8 mL/kg/PBW can be an issue in some ICUs. With this in mind, most modern ventilators allow the practitioner to view the tidal volume as expressed as mL/kg/PBW. Higher tidal volumes can occur during pressure-cycled ventilation modes with increased inspiratory effort and improving (i.e., increasing) compliance of the lungs, chest wall, or both.

Setting and Responding to Ventilator Alarms

ROLE OF RESPIRATORY CARE PRACTITIONERS IN THE INTENSIVE CARE UNIT

Although all health care professionals working in the ICU should be knowledgeable about ventilator alarms, respiratory care practitioners have the primary responsibility for ventilator management and for setting all alarms. These individuals (generally identified as registered respiratory therapists [RRTs] or certified respiratory therapists [CRTs]) have had specialized training to deal with ventilators, ventilator quality control, and ventilator-related problems. They serve as resource persons for ventilator alarms in the ICU. If the ventilator's alarms are set incorrectly, they can lead to false alarms—that is, they may activate in the absence of a true ventilator mishap or patient event. These false alarms, often called *nuisance alarms,* can compromise patient safety if they lead to the failure of ICU staff to respond to true events.

THE ALARM PACKAGE

Microprocessor-based ventilator alarms can be visual, audible, or both. They also usually signal a message to direct the clinician to the problem. An audio alarm may have been initiated, but by the time the caregiver reaches the bedside, the situation may have corrected itself. Most ventilators are equipped with a memory display, which identifies the reason why the alarm originally activated. The alarm package on microprocessor-based ventilators also has a priority level to alert the practitioner to the seriousness of the alarm and, consequently, to the promptness required in responding to the alarm (see Table 47.1).

BUILT-IN VENTILATORY SAFETY DEVICES

All ventilators have certain safety devices built in to ensure patient safety. Non–microprocessor-based ventilators have only pressure-monitoring capabilities. Microprocessor ventilators continuously perform a self-assessment. Although manufacturers have safety features unique to their own products, some are common among most brands in use. These safety devices are usually designed to protect the patient from any harmful effects caused by ventilator malfunction.

Backup apnea ventilation refers to a built-in safety device that serves two main functions: first, it provides as an emergency mode of ventilation when the microprocessor senses a ventilator malfunction; second, it activates if the ventilated patient becomes apneic for a period longer than the set parameters allow. For some ventilators, the clinician has the option to choose these parameters. For others, the parameters are set by the manufacturer.

The ventilator and the ventilator circuit are a closed system—that is, they are closed to atmospheric pressure. As such, all ventilation and gas sources are provided via the ventilator's pneumatic system. However, if the ventilator becomes inoperative and the patient is still capable

of spontaneous breathing, modern ventilators have a safety valve, which opens the ventilator circuit to ambient air, thus allowing the patient to breathe unassisted by the ventilator.

Most microprocessor-based ventilators require a "preuse test" before they can be used to ventilate a patient. This assures proper calibration and function beforehand. This test also evaluates the ventilator circuit, making sure all connections are properly sealed and preventing unwanted air leaks. It even measures the compliance of the circuit, which allows the ventilator to increase its generated tidal volume to compensate for the volume needed to expand the tubing during inspiration.

RESPONDING TO VENTILATOR ALARMS

When responding to ventilator alarms, one's first priority must be to ensure patient safety. A good rule of thumb is to ventilate the patient manually by use of a bag-valve mask apparatus (i.e., a manual resuscitator) if one is in doubt about the adequacy of the patient's ventilatory support. Likewise, if a potentially dangerous situation cannot be corrected immediately, the patient should be promptly switched from ventilator to a manual resuscitator. After ensuring patient safety, one should take a general stepwise approach when responding to ventilator alarms (see Figure 47.1).

An annotated bibliograpy can be found at www.expertconsult.com.

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This is a comprehensive review detailing all things relevant to mechanical ventilation.

CHAPTER 48

Weakness Developing in the Intensive Care Unit Patient

Shawn J. Bird

There are numerous causes of generalized weakness that may develop in patients in the intensive care unit (ICU). Weakness may result from dysfunction of the central nervous system (CNS), the peripheral nervous system, or both. Causes of weakness that developed de novo in the setting of critical illness are discussed here. Disorders that develop in the ICU setting are generally separated from disorders that produce weakness severe enough to result in ICU admission, such as myasthenia gravis or the Guillain-Barré syndrome (see Chapter 67). Patients with a preexisting neuromuscular disorder, such as amyotrophic lateral sclerosis, may also present for ICU admission with acute weakness in the setting of another illness (such as infection).

The differential diagnosis of *acute, generalized weakness* is aided by clues from the history and neurologic examination, as summarized in Tables 48.1 and 48.2. If it is unknown whether the weakness predated the current ICU period, then the differential diagnosis should also include the entities that may produce weakness that necessitates ICU care (see Table 67.2).

If the patient develops *unilateral weakness (hemiparesis)*, then acute structural lesions such as stroke or intracerebral hemorrhage are most common. A seizure, particularly when prolonged, may also produce prolonged unilateral weakness (Todd's paralysis). It is also important to consider spinal cord compression, in that lateral spinal cord compression may produce predominantly unilateral weakness.

TABLE 48.1 ■ **Acute, Unilateral Weakness Developing in the ICU Patient**

Cause by Localization	Suggestive Clinical Features	Diagnostic Tests
Stroke—ischemic or hemorrhagic	Face and arm often weaker than leg Risk factors, such as atrial fibrillation, MI, endocarditis or bleeding diathesis/anticoagulation (ICH)	MRI (brain)*
Seizure—after a pronged seizure (Todd's paralysis) or with nonconvulsive status epilepticus	History of prior seizure(s) or witnessed seizure Underlying structural lesion common	EEG† and MRI (brain)
Spinal cord—lateral compression by epidural abscess, tumor, or hemorrhage	Back or neck pain No involvement of face Sensory level (see Figure 102-1) Arms may be spared in thoracic or lumbar lesions	MRI (cervical, thoracic, or lumbar spine)

*Other studies commonly include CTA or MRA of head and neck, echocardiogram, telemetry, and carotid ultrasound.
†Frequently requires continuous EEG monitoring.
MI, myocardial infarction; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; EEG, electroencephalography; CTA, computed tomographic angiography; MRA, magnetic resonance angiography.

TABLE 48.2 ■ **Acute, Generalized Weakness Developing in the ICU Patient***

Cause by Localization	Suggestive Clinical Features	Diagnostic Tests
Brain†	Unresponsiveness with quadriparesis	
Encephalopathy (sepsis, sedating drug, renal or hepatic failure)	Severe infection Known renal or hepatic disease	Blood cultures; imaging for infections Renal and hepatic blood studies
Bilateral structural lesion (strokes, SAH, herniation secondary to increased intracranial pressure)	Onset with unilateral weakness Asymmetrically enlarged pupil	CT scan (brain), MRI (brain)
Nonconvulsive status epilepticus	History of seizures; rapid fluctuation of responsiveness	Prolonged EEG monitoring
Brain Stem	Ocular motor abnormalities common	
Brain stem stroke	May be unresponsive or awake	MRI (brain)
Central pontine myelinolysis	Rapid correction of severe hyponatremia	MRI (brain)
Spinal Cord	Sensory level; early urinary retention; spares cranial muscles	
Acute epidural compression (abscess, hemorrhage, tumor)	History of infection, tumor or bleeding Back or neck pain Weakness may be limited to the legs (in thoracic cord lesions)	MRI (cervical, thoracic, or lumbar spine)
Other causes (cord hemorrhage)	Risk for hemorrhage	MRI (cervical or thoracic spine)
Peripheral Nerve	Weakness, with sensory and reflex loss	
Critical illness polyneuropathy‡	Develops after period of crucial illness	EMG; NCS
Neuromuscular Junction	Weakness, without sensory or reflex loss	
Prolonged pharmacologic neuromuscular blockade	History of neuromuscular blocking agents and renal or hepatic dysfunction	Train-of-five; or EMG with RNS studies
Hypermagnesemia	History of renal failure	Serum magnesium
Muscle	Weakness, without sensory or reflex loss	
Critical illness myopathy‡	Develops after period of crucial illness; often history of corticosteroid or NMBA use	EMG
Severe hypokalemia	History of hypokalemia, diuretic use, or renal tubular acidosis	Serum potassium

*This is for de novo weakness in the ICU setting; for a full differential diagnosis of weakness add Table 67.2.
†The level of obtundation should be significant enough to produce quadriparesis with these disorders (see text).
‡Critical illness (i.e., severe sepsis) is the presumptive cause of these disorders.
SAH, subarachnoid hemorrhage; CT, computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalography; EMG, electromyography; NCS, nerve conduction studies; RNS, repetitive nerve stimulation; NMBA, neuromuscular blocking agent.

If the weakness is generalized, it is important to take into account the patient's level of consciousness. Patients with severe sepsis or drug-induced encephalopathy will have limb weakness in proportion to their degree of unresponsiveness. This is also the case with patients with severe, bilateral structural brain disease (e.g., bilateral strokes or a herniation syndrome), or encephalitis. In a patient who is responsive, a brain disorder is unlikely to be the cause of significant quadriparesis. In this circumstance, involvement of the spinal cord or the peripheral nervous system (e.g., motor neuron, nerve, neuromuscular junction, or muscle) should be suspected. Spinal cord compression is particularly important to recognize, in that it is treatable if identified early.

Acute Neuromuscular Weakness Developing in an Intensive Care Unit Patient

The development of severe, acquired neuromuscular weakness is common in the ICU. The two syndromes that account for the majority of cases of such acquired weakness are *critical illness polyneuropathy* (CIP) and *critical illness myopathy* (CIM). These disorders contribute significantly to prolonged ventilator dependence. The mean increase is ~12 ventilator days in ICU patients with one of these disorders compared to those without CIP or CIM.

Recognizing that significant limb weakness, or the inability to wean the patient from mechanical ventilation, is due to an ICU-acquired neuromuscular cause is helpful in several ways. It may prevent unnecessary investigative studies, such as extensive brain or spinal cord imaging. Weaning from the respirator may be slowed considerably and extubation may be appropriately delayed until respiratory muscle strength and ability to cough are adequate. The identification of CIP or CIM as the cause of the weakness, rather than brain injury, avoids placing an erroneously pessimistic prognosis on such patients.

Electrodiagnostic studies (electromyographic [EMG] and nerve conduction studies) are the most effective way to confirm the presence of CIM or CIP and to quantify the severity of the disorder. Nerve and muscle biopsies are invasive and are not generally performed in the ICU setting, unless there is suspicion of another disorder that is best identified pathologically (e.g., vasculitis or myositis).

The risk factors for both CIP and CIM overlap, so many patients have a variable combination of both disorders. The incidence of CIP or CIM is high in critically ill patients (e.g., ~50% or higher incidence in patients with severe sepsis who are in the ICU for more than a week). Of these patients, ~10% have only CIP, 10% have only CIM, and 80% have both. The major risk factor for the development of CIP or CIM is the presence of the systemic inflammatory response syndrome (SIRS) (Chapter 10). Measures of illness severity (Apache II or III score, presence of SIRS, or organ failure assessment scores) correlate with the development of CIP/CIM. The likelihood of developing CIP, CIM, or both is strongly influenced by the severity of illness. In addition to sepsis, there is an association between receiving high-dose corticosteroids and nondepolarizing neuromuscular blocking agents (NMBAs) with CIM.

Critical Illness Polyneuropathy

CIP is a sensory-motor axonal nerve disorder that may develop in the setting of SIRS or sepsis, usually in its severe form (e.g., sepsis with multiorgan failure). The clinical features of CIP are limb weakness, often predominantly distal in distribution, and failure to wean from mechanical ventilation, which may be the first recognized manifestation (Table 48.3). Reflexes are reduced or absent, particularly in the lower extremities. Sensory loss can be present, but it is usually difficult to identify reliably in patients unable to cooperate with the examination because of coexistent encephalopathy or sedation. Cranial nerve involvement is rare in CIP and should suggest the possibility of an alternative neurologic disorder.

Electrophysiologic studies of CIP are those of an axonal sensory-motor neuropathy. Nerve conduction studies (NCSs) are characterized by reduced sensory and motor response amplitudes reflecting the underlying axonal loss. There are no features that suggest demyelination, as are seen in the Guillain-Barré syndrome (GBS) (see Chapter 67). In those with severe CIP, phrenic nerve conduction is often absent and needle EMG examination of the diaphragm can demonstrate denervation.

The pathogenesis of CIP is speculative because no specific toxin, infectious agents, or nutritional deficiencies have been identified in patients with this disorder. One view is that cytokines and free radicals associated with SIRS adversely affect the peripheral nerve microcirculation. This, in turn, produces endoneurial hypoxia or ischemia or both and distal axonal degeneration.

TABLE 48.3 ■ **Critical Illness Polyneuropathy (CIP) and Critical Illness Myopathy (CIM)**

	Critical Illness Polyneuropathy	Critical Illness Myopathy
Risk factors	Sepsis or SIRS	Sepsis or NMBAs and corticosteroids
Clinical findings	Sensory and motor deficits	Purely motor
Serum studies	CPK normal	CPK normal to slightly ↑
Pathology of biopsied tissue*	Nerve—axonal loss Muscle—denervation	Nerve—normal Muscle—patchy myosin loss; minimal necrosis
Electrodiagnostic Studies		
Nerve conduction studies	↓ Sensory and motor potential amplitudes	Normal sensory potentials ↓↓ Motor potential amplitudes
Needle EMG		
Spontaneous activity	Yes; often prominent	None or sparse
MUP morphology	Normal to long-large	↓ Amplitude and ↓ duration
MUP recruitment	Decreased (neurogenic)	Early full (myopathic)
Muscle excitability studies†	Normal	Absent or ↓↓
Prognosis	Slow recovery with severe axonal loss	Often rapid recovery over weeks to 3 months

*Not usually performed in clinical practice (see text).
†Not available at most centers.
SIRS, systemic inflammatory response syndrome; NMBAs, neuromuscular blocking agents; CPK, creatine phosphokinase; MUP, motor unit potential.

Critical Illness Myopathy

As with CIP, the clinical presentation of CIM is that of limb and respiratory muscle weakness that develops acutely but is often difficult to recognize early because of coexistent encephalopathy, sedation, or both. The weakness varies from mild to complete quadriplegia. The weakness is *not* in a length-related pattern—that is, where distal muscles are weakest—typical of CIP and most neuropathies (see Table 48.3). In patients with CIM, there is usually as much proximal limb weakness as there is distal. Respiratory muscles are frequently involved, and this delays weaning from mechanical ventilation. Failure to wean from mechanical ventilation may be the first recognized manifestation. Neck flexor or facial muscle weakness may be present, but the presence of ophthalmoparesis should suggest the existence of another disorder. Sensation is spared but often cannot be clinically evaluated in an encephalopathic, sedated, and intubated patient. As with other myopathies, deep tendon reflexes are decreased in parallel with the decrease in strength.

The serum creatine kinase (CK) is elevated in less than half of the reported patients, and usually only mildly. As with CIP, the electrophysiologic studies are key to confirming the presence of CIM. Motor nerve conduction studies in patients with CIM often differ from that found in most myopathies. The motor response amplitudes are reduced, or even absent, when recording from distal limb muscles. In many patients the motor response durations are abnormally prolonged. There is preservation of sensory nerve action potential amplitudes, unless there is coexistent CIP or preexistent neuropathy.

Muscle biopsy is invasive and not routinely performed for the diagnostic confirmation of CIM. However, the muscle pathology in CIM has been shown to commonly have a characteristic patchy loss of myosin thick filaments. This is the most distinctive pathologic finding of CIM.

The mechanisms involved in producing muscle weakness in CIM are multifactorial. Sepsis and the use of nondepolarizing neuromuscular blocking agents and high-dose corticosteroids may result in myosin loss and changes in other structural proteins through several cellular mechanisms. Impaired muscle membrane excitability probably plays a more significant role in producing weakness in the acute stage. Muscle membrane inexcitability is likely due to abnormal sodium channel inactivation.

Persistent Pharmacologic Neuromuscular Blockade

The effects of neuromuscular blocking agents (NMBAs) (Chapter 6) can persist in individual patients, creating unexpected weakness and inability to wean from mechanical ventilation. Metabolic derangements, particularly renal failure, can slow the clearance of certain neuromuscular blocking agents and their active metabolites, producing prolonged paralysis. If prolonged quadriparesis due to a NMBA is suspected, this effect is easily detected with nerve conduction studies with repetitive nerve stimulation. Prolonged blockade may last for days and should be considered in any patient who remains weak after discontinuation of NMBAs. Weakness should not persist beyond 2 weeks after stopping the blocking agent, however, and typically lasts for only a few days.

Treatment and Prognosis of CIP and CIM

There is no specific pharmacologic treatment for either critical illness polyneuropathy or critical illness myopathy. Nevertheless, the first step—recognizing the presence of one of these disorders—often improves management. Prevention of CIP and CIM may be feasible if one can avoid adding extra risk factors, such as high-dose glucocorticoid steroids and NMBAs, to the medical management of critically ill patients.

Recovery from CIM generally has an excellent prognosis. Most patients with CIM have recovery to near-complete or complete functional independence within 1 to 3 months. Neurologic recovery from CIP is a bit more variable, although it is also good overall. As with recovery from the Guillain-Barré syndrome, recovery in CIP depends on the degree of axonal degeneration. In severe cases of CIP with a significant amount of axonal loss, the recovery time is longer and distal motor and sensory deficits may persist indefinitely.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 49

Advanced Cardiac Life Support (ACLS) and Therapeutic Hypothermia

David A. Fried ■ Marion Leary ■ Benjamin S. Abella

Sudden cardiac arrest (SCA) is defined as the immediate cessation of mechanical cardiac function and the concomitant global loss of blood flow. SCA is a leading cause of death in the United States with approximately 300,000 Americans succumbing to SCA each year. Advanced Cardiac Life Support (ACLS) represents a set of highly time-sensitive therapeutic maneuvers used to support and ultimately restore circulation (see Figure 49.1 for overview of the SCA survival time line). ACLS includes cardiopulmonary resuscitation (CPR), endotracheal intubation, electrical defibrillation for appropriate cardiac rhythms, and the use of specific pharmacologic interventions. ACLS algorithms (see Appendix D for ACLS algorithms) are widely used during both in-hospital SCA (by trained nurses and physicians) and out-of-hospital SCA (by ambulance personnel). ACLS certification is required for a large number of health care providers.

A multisite study from 2008 evaluating cardiac arrest survival outcomes revealed a wide range of survival to hospital discharge rates in the United States, from 3% to 16% with an overall 8% survival for out-of-hospital cardiac arrest. Survival from in-hospital cardiac arrest is somewhat higher, with a large registry study documenting 18% survival to hospital discharge. Since the development and implementation of rapid response teams (RRTs; also known as medical emergency teams or METs [see Chapter 110]) to respond to impending arrest events in the hospital, the demographics of in-hospital cardiac arrest has shifted, with fewer SCA events on the general wards and more events taking place in intensive care units (ICUs). The overall impact of RRTs on SCA survival, however, remains controversial and a topic of ongoing investigation.

Although the sequence of actions required in ACLS had been generally considered complete once a patient had regained a pulse, the introduction of a powerful post-resuscitation treatment option, therapeutic hypothermia (TH), has broadened the scope of resuscitation care. TH, the intentional lowering of core body temperature after initial resuscitation, has been shown to improve both survival and neurologic outcomes following SCA. This chapter provides an overview of cardiac arrest resuscitation care as well as important aspects of post-resuscitation care including TH. Although reference will be made to the ACLS protocols and guidelines established by the

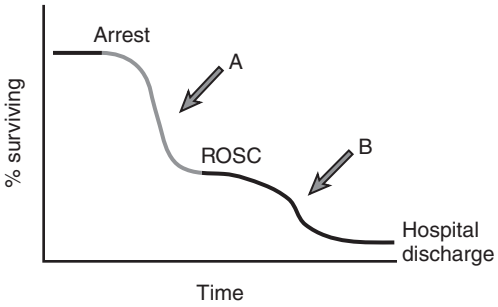


Figure 49.1 Schematic time line of survival following sudden cardiac arrest. Note the two time periods where mortality occurs: **A,** during resuscitation, where ACLS interventions take place; **B,** after return of spontaneous circulation (ROSC), where therapeutic hypothermia has a role to improve outcomes.

TABLE 49.1 ■ **Cardiopulmonary Resuscitation Quality Parameters**

Parameter	Guideline
Ventilation rate (intubated)	8–10 breaths per minute
Compression to ventilation ratio (nonintubated)	30:2 CCs to breaths
Compression rate	100 CCs per minute
Compression depth	1.5–2 inches for each CC
Release/recoil	Full release from chest after CC
Pauses	Minimize all pauses

CC, chest compression.

American Heart Association (AHA), they will not be restated here. Clinicians should consult ACLS manuals and AHA reference materials for specific protocol information (see Appendix D for 2010 ACLS algorithms).

Cardiopulmonary Resuscitation

A crucial first step to restoring circulation is the immediate performance of cardiopulmonary resuscitation (CPR), a technique that took its modern form in the 1960s. Promptly delivered CPR, performed correctly and effectively, can increase the chances of survival two- to threefold. Consensus resuscitation guidelines promulgated by the AHA recommend chest compressions at a rate of 100 per minute and ventilations, using mouth-to-mouth or bag-valve-mask technique, with approximately 8 to 10 breaths per minute. The AHA recommends "pushing hard and fast," with compression depth of 1.5 to 2 inches of chest deflection in adults, ensuring full chest recoil and minimizing interruptions in chest compressions (see Table 49.1 for key aspects of correct CPR performance). Recommendations for basic life support (BLS) care changed in 2005, from compression-to-ventilation cycles of 15:2 to the currently recommended 30:2 for adult patients, in order to circulate as much oxygenated blood to vital organs as possible. It is estimated that CPR only generates 20% to 30% of normal cardiac output, and blood flow depends greatly on the quality of this intervention. For every minute CPR is not performed after the heart has stopped, the chances of survival decrease approximately 10% to 15%.

Monitoring the Quality of CPR

Although CPR seems simple to perform, both in-hospital and out-of-hospital investigations have shown that incorrectly or suboptimally performed CPR is common in actual practice and can compromise patient survival. One study found that rescuers' chest compression rates were less than 90 per minute 28% of the time, compression depth was too shallow in 61% of compressions, and ventilation rates were often too high. A number of studies have shown that defibrillation efficacy and successful restoration of a pulse are sensitive to compression rate and depth. Additionally, an out-of-hospital investigation showed that hyperventilation during CPR may significantly decrease survival. To address these major discrepancies in cardiac arrest care, a variety of devices have been developed with a goal of improving CPR quality by providing rescuers with immediate audio or visual feedback on CPR performance. These devices are either freestanding or incorporated into standard defibrillators; they have a "pad" or "puck," which is outfitted with an accelerometer and force detector. The rescuers perform CPR through these sensing pads, placed on the chest of the patient in the same place rescuers normally put their hands for CPR. Another modality used to improve CPR quality has been simple metronome devices—for example, a ventilatory-assist

device currently in use flashes an indicator light at a rate of 10 per minute, prompting appropriate ventilation rates by rescuers.

A more dramatic approach to improving CPR quality has been to automate the process via devices that provide battery or compressed air–powered chest compressions by either a circumferential belt around the victim's chest or a piston device positioned over the sternum, respectively. Initial studies suggest that human CPR with feedback devices and mechanical CPR devices may improve performance and possibly survival from cardiac arrest, although further confirmation is required. An additional advantage of the CPR feedback approach is the ability to record CPR performance for later quality assurance processes and educational purposes. Debriefing has been shown to improve both CPR quality and initial resuscitation success.

30:2 versus 15:2 versus Hands-Only CPR

The 2005 AHA guidelines implemented an important change in the compression-to-ventilation ratio for basic life support CPR, from 15:2 to 30:2. This change acknowledged the then newly recognized significance of decreasing the "no flow time," or the time the rescuer is not compressing on the chest despite a continued pulseless state. Frequent pauses during CPR decrease the likelihood that a defibrillatory shock will be successful and have also been shown in animal studies to decrease the probability of pulse restoration. For intubated patients (and therefore CPR performed by trained hospital personnel), the AHA recommendation is to perform compressions at 100 per minute while simultaneously ventilating at a rate of 8 to 10 per minute. For CPR performed by the lay public, based on data from a number of out-of-hospital SCA cohort studies, the AHA has endorsed the use of a BLS variant without ventilations, known as "hands-only CPR," with the notion being that mouth-to-mouth ventilation is both difficult to perform and an important deterrent to performing CPR at all. Although this notion of omitting ventilations certainly does not apply to the in-hospital SCA patient population, there is growing evidence that compressing the chest efficiently and effectively should be prioritized over ventilations at least initially during resuscitation efforts, and therefore the quality of compressions should be emphasized.

Defibrillation

Defibrillation, the delivery of a therapeutic electrical shock to the myocardium, is the primary therapy available to treat ventricular fibrillation and pulseless ventricular tachycardia (VF/VT), the two most common arrhythmias associated with out-of-hospital cardiac arrest. Successful defibrillation depolarizes most of the functioning myocardium, momentarily inducing a pause in myocardial conduction and in principle allowing the sinoatrial node to regain control and initiate a normal perfusing rhythm. As a practical matter, defibrillation is performed either directly via electrode paddles or pads applied to exposed myocardium (internal paddles) or indirectly via the patient's chest (external pads or paddles). Defibrillation can be performed via a *manual* defibrillator, in which a rescuer identifies a rhythm and determines whether a shock is indicated, or an *automatic* defibrillator, which electronically determines the cardiac rhythm and performs the shock without rescuer input.

Automatic external defibrillators (AEDs) are commonly found installed in airports or other public settings and have been shown to dramatically improve survival from out-of-hospital cardiac arrest. Although often successful when administered promptly and correctly, defibrillation success diminishes quickly when the shock is delayed. This results because shockable rhythms tend to decay within several minutes toward a less shockable form of ventricular fibrillation or asystole. Delayed defibrillation occurs during both out-of-hospital and in-hospital cardiac arrest resuscitation and is associated with poor outcomes from SCA.

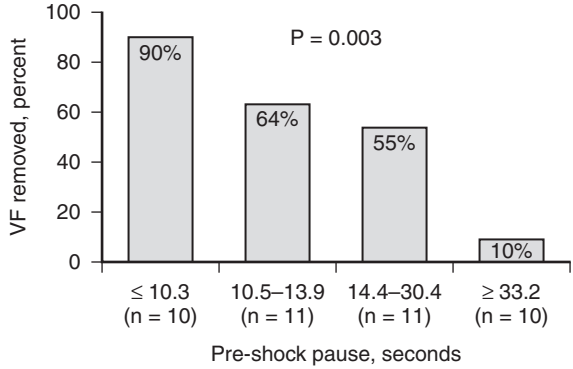


Figure 49.2 The effect of pauses in CPR before defibrillation ("pre-shock pauses") on shock success. Note the highly time-sensitive nature of these pauses, which are common in clinical practice. VF, ventricular fibrillation. *(Adapted from Edelson DP, Abella BS, Kramer-Johansen J, et al: Effects of compression depth and pre-shock pauses predict defibrillation failure during cardiac arrest. Resuscitation 71:137-145, 2006.)*

BIPHASIC VERSUS MONOPHASIC DEFIBRILLATION

Until the early 2000s, most defibrillators used a monophasic waveform with current flowing in one direction between electrodes. Newer research supports the use of a biphasic waveform, where current polarity reverses from one electrode to the other during the shock. Biphasic defibrillation has a higher first shock success rate than monophasic defibrillation for cessation of VF/VT. Successful biphasic defibrillation requires less energy than monophasic shocks, with a maximum recommended charge of 200 joules (J) for biphasic versus 360 J for monophasic defibrillation. Additionally, biphasic defibrillation may result in less shock-induced myocardial dysfunction, which could be partly responsible for subsequent restoration of cardiac output.

Current ACLS guidelines state that health care providers should use a biphasic defibrillator if available and select the energy setting recommended by the manufacturer (generally either 150 or 200 J). If the specific device parameters are unknown, providers should use 200 J for the first shock and an equal energy "dose" for subsequent shocks. For monophasic defibrillators, 360 J is the generally accepted highest charge level. The most effective energy level is not currently known, nor is it known whether a fixed or escalating energy level is best when multiple shocks are required.

CPR INTERACTIONS WITH DEFIBRILLATION

Unless immediate defibrillation is available within 4 to 5 minutes of VF/VT onset, studies have suggested that a patient's chance of survival increases when CPR is performed before attempting defibrillation. In addition, the quality of the delivered CPR affects defibrillation success. Specifically, pauses in CPR and chest compressions with inadequate depth decrease the probability of successful defibrillation (Figure 49.2). This indicates that the longer myocardial tissue remains without blood flow, the less likely a defibrillatory shock will succeed in restoring a normal sinus rhythm. CPR may therefore act as a primer by restoring some circulation to the heart before defibrillation. The 2005 AHA consensus guidelines for CPR recommend that high-quality compressions continue while the defibrillator is being prepared and charged. This is a safe, proven method to reduce preshock pauses.

Ever since the introduction of defibrillation, common sense has dictated that physical contact with the patient should be avoided during a shock in order to prevent stray electrical current from injuring the rescuer. Although the risk of inadvertent shock to a rescuer exists if a rescuer is still in

TABLE 49.2 ■ **Pharmacologic Therapy during Advanced Cardiac Life Support**

Name and Type	Use (Indication and Dose)
Epinephrine: vasopressor, positive inotrope	Indication: any SCA 1 mg IV bolus q3–5min
Atropine: anticholinergic agent	Indication: asystole, bradycardic PEA 0.5–1.0 mg IV bolus, q3min
Vasopressin: vasopressor, antidiuretic	Indication: any SCA 40 IU once initially
Amiodarone: class III antiarrhythmic	Indication: refractory VF 300 mg IV bolus
Lidocaine: class 1b antiarrhythmic	Indication: refractory VF 1 mg/kg IV bolus

SCA, sudden cardiac arrest; IV, intravenous; IU, international units; PEA, pulseless electrical activity; VF, ventricular fibrillation.

contact with the patient during defibrillation, the chance of this occurring is very small and new evidence suggests that the risk may be negligible. Some experts suggest that defibrillation could be performed, in theory, by a gloved rescuer without stopping CPR and therefore maximizing the chance for successful shock. Current guidelines still recommend that all rescuers cease contact with the patient before defibrillation, as further research is needed to examine the safety of hands-on defibrillation.

DEFIBRILLATOR PAD POSITIONING

Defibrillation requires the placement of two electrodes on the patient's chest in a position that allows electrical current flows between them to maximize current through the myocardium. The electrodes are built into paddles or hands-free adhesive pads, which are placed either anterior-apical (one pad at the right upper sternal border and the other at the left midaxillary line) or anterior-posterior (one pad on the left side of the chest directly over the heart and the other on the left side of the back). Adhesive pad electrodes placed anterior-apical are the preferred combination during cardiac arrest resuscitation for practical reasons. Adhesive pads allow hands-free operation, decreasing pauses in CPR, and are in general easier and more efficient to use.

Medications

Different cardiac arrest rhythms require specific pharmacologic approaches in addition to CPR and defibrillation. Some medications, such as epinephrine, have been central to ACLS care for decades. However, it is important to note that the data supporting most of these medical therapies for SCA are sparse at best, and very few ACLS medications have the support of randomized controlled trials. A comprehensive review of pharmacologic therapy for SCA is outside the scope of this chapter but is reviewed elsewhere (see the Nolan et al review in the bibliography); common medications and their uses are summarized in Table 49.2.

Epinephrine

Epinephrine, a small molecule endogenously produced in the adrenal glands that acts via cell surface adrenergic receptors, has wide-ranging effects and is employed during resuscitation care for

all cardiac arrest rhythms. Epinephrine acts via alpha-adrenergic receptors to increase inotropic function and coronary perfusion pressure (CPP), which may play a role in increasing the probability of successful resuscitation. Although epinephrine increases CPP, its action via beta-adrenergic receptors may actually be harmful during cardiac arrest because they have properties that increase oxygen consumption and decrease subendocardial perfusion. Together it is thought that alpha and beta-adrenergic agonists may increase myocardial ischemic injury. Indeed, an older algorithm for "escalating dose" epinephrine in which SCA was treated with higher doses of epinephrine was shown to worsen post-resuscitation physiology and survival outcomes. Furthermore, a study of out-of-hospital SCA that randomized care to include or not include epinephrine dosing did not demonstrate a statistically significant improvement in survival with epinephrine use. Nonetheless, the current ACLS recommendation (as of 2010, see Appendix D) is to administer epinephrine 1 mg IV push every 3 to 5 minutes during active cardiac arrest resuscitation.

ATROPINE

Atropine, an anticholinergic agent and muscarinic receptor antagonist, increases chronotropy of the sinoatrial node and suppresses influence from the vagus nerve at the atrioventricular node (so-called vagolytic action). Atropine therefore increases the heart rate and may be useful during bradycardic or asystolic cardiac arrest. Atropine is not indicated during resuscitation from pulseless electrical activity (PEA) cardiac arrest, unless the arrest rhythm is bradycardic. Atropine is given as a 0.5- to 1-mg IV bolus and can be repeated every 3 minutes up to a dose of 0.04 mg/kg.

VASOPRESSIN

Vasopressin is an endogenously produced peptide hormone that is released by the posterior pituitary and is also known as antidiuretic hormone (ADH). During physiologic stress, vasopressin increases peripheral vascular resistance, thereby enhancing blood flow to the heart, brain, and kidneys. This enhanced blood flow may be useful during resuscitation efforts. A large multicenter study by Wenzel et al showed that, although there was no difference in survival when SCA patients were randomized to epinephrine or vasopressin during resuscitation, there was a significant difference in survival to discharge when vasopressin was used for asystolic arrests (4.7% with vasopressin versus 1.5% with epinephrine). However, subsequent work has cast doubts on the benefit of vasopressin. It is considered an option to replace an initial dose of epinephrine, but this alternative is not in widespread use. The recommended dose of vasopressin during resuscitation is 40 international units (IU) given once during initial resuscitation efforts.

ANTIARRHYTHMIC DRUGS

Although vasopressors such as epinephrine or vasopressin improve blood flow during CPR, antiarrhythmic drugs act to suppress or modify VF/VT. A wide variety of antiarrhythmic agents have been proven to have particular effects in patients with spontaneous circulation, but studies in SCA are limited. Shock refractory ventricular fibrillation is defined as VF that persists after the delivery of three or more defibrillation attempts—and it is for this particular condition that antiarrhythmics such as lidocaine or amiodarone may be useful.

Amiodarone

Amiodarone is a class III antiarrhythmic agent, a potassium channel blocker that increases the duration of action potentials, and it is currently the drug of choice for patients with shock refractory VF. It also exhibits properties of the other three classes of antiarrhythmic drugs. Studies have shown amiodarone to increase survival to hospital admission for out-of-hospital VF/VT patients, but few data exist suggesting that amiodarone improves survival to hospital discharge. Other

investigations have shown that, since its widespread acceptance, the use of amiodarone during in-hospital resuscitation is increasing, but no survival benefits have yet been noted with the use of this medication. Guidelines recommend administering amiodarone as a 300-mg IV bolus after the third shock in patients with VF/VT, although some experts recommend its use after the first or second failed shock attempt.

Lidocaine

Lidocaine is a local anesthetic and a class 1b antiarrhythmic, a sodium channel blocker that shortens the duration of action potentials. As an antiarrhythmic, it is used to suppress ventricular arrhythmias. When administered prophylactically, lidocaine has been shown to prevent VF in patients with acute myocardial infarction. Since the 1990s, AHA guidelines have recommended the use of lidocaine for shock refractory VF. When amiodarone is not available, lidocaine 1 mg/kg IV can be used as an alternative regimen.

Therapeutic Hypothermia

Since the inception of CPR and defibrillation, there have been few breakthroughs that increase survival from cardiac arrest. Therapeutic hypothermia (TH), when induced promptly after resuscitation from cardiac arrest, has been shown to improve the probability of overall survival as well as neurologic recovery. It is believed that TH acts at the level of postcardiac arrest–induced reperfusion injury, a complex pathophysiology that is initiated by the abrupt return of blood flow to ischemic tissues. Experimental models have implicated reactive oxygen species generation, mitochondrial dysfunction, and widespread inflammatory disinhibition in reperfusion injury. TH likely attenuates each of these mechanisms to varying extents.

Implementation of TH involves three phases: induction, maintenance, and rewarming. Induction begins when patients are cooled to a temperature of 32.0° to 34.0° C, a process that generally takes several hours. This lowered core temperature is then maintained for 12 to 24 hours from the time the target temperature was reached. Rewarming is performed slowly over another period of 12 to 24 hours. Beyond its cardioprotective and neuroprotecive effects, TH has also been show to significantly lessen ICU stays for out-of-hospital cardiac arrest patients. TH is a topic of intensive research in both animal models and the clinical setting.

In 2002, two landmark randomized controlled clinical trials evaluated the use of TH versus maintaining normothermia in adults, all of whom had out-of-hospital cardiac arrests with initial VF/VT—the European multicenter Hypothermia after Cardiac Arrest (HACA) trial and another multicenter study by Bernard et al. In both, patients were cooled to a temperature between 32.0° and 34.0° C for 12 to 24 hours. Both showed significantly increased survival to discharge and improved neurologic outcomes in the patients randomized to TH treatment (see Table 49.3). The HACA investigators also examined neurologic survival at 6 months and found that this mortality benefit persisted. On the basis of this evidence, the AHA recommends using TH as a postarrest intervention after VF/VT (class IIa recommendation) and after other arrest rhythms (class IIb recommendation) in patients who remain comatose after successful circulatory resuscitation from cardiac arrest.

PATIENT SELECTION FOR HYPOTHERMIA TREATMENT

Although there is no uniformly accepted list of exclusion and inclusion criteria for TH treatment, a growing consensus is emerging on patient selection for this critical care intervention. The purpose of TH is to mitigate brain injury from reperfusion injury, so patients who promptly awaken after SCA (for example, those who are rapidly defibrillated and are alert minutes after resuscitation) are generally considered to have an excellent prognosis and do not require TH induction. Because coagulopathy is a potential side effect of TH, many hospital protocols for TH exclude patients who are either immediately postoperative or have clinically significant bleeding. Some

TABLE 49.3 ■ **Summary of Therapeutic Hypothermia Clinical Trials**

Trial	Hypothermia No. Alive/Total	Normothermia No. Alive/Total	Risk Ratio (95% CI*)	P Value
Alive at hospital discharge with favorable neurologic recovery				
HACA, 2002	72/136 (53%)	50/137 (36%)	1.51 (1.14–1.89)	0.006
Bernard et al, 2002	21/43 (49%)	9/34 (26%)	1.75 (0.99–2.43)	0.052
Hachimi-Idrissi, 2001	3/16 (19%)	0/17 (0%)	7.41 (0.83–∞)	0.15
Summary estimate			1.68 (1.29–2.07)	
Alive at 6 months with favorable neurologic recovery				
HACA, 2002	71/136 (52%)	50/137 (36%)	1.44 (1.11-1/76)	0.009

*CI, confidence interval; HACA, Hypothermia after Cardiac Arrest trial.

Adapted from Holzer M, Bernard SA, Hachimi-Idrissi S, et al: Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. Critical Care Med 33:414-418, 2005.

TABLE 49.4 ■ **Potential Adverse Effects from Hypothermia**

Bradycardia
Coagulopathy/platelet dysfunction
Shivering
Hypokalemia
Hypomagnesemia
Cold diuresis/intravascular volume depletion
Increased infection risk

This list represents the most commonly observed adverse effects; other phenomena, such as more significant arrhythmias, can be observed if patients are overcooled (< 32.0° C).

clinicians may consider that patients who have poor neurologic status (e.g., comatose or nonverbal or with severe dementia) *before* SCA not be candidates for TH. Although randomized controlled trial data supporting use of TH in children are not yet available, many centers include pediatric cardiac arrest patients as eligible for postarrest TH.

HYPOTHERMIA: ADVERSE EFFECTS

Potential adverse effects of cooling a patient to 32.0° to 34.0° C are varied but have been found to have a modest impact during TH intervention. The most common cardiac adverse effect of TH, bradycardia, is generally of little hemodynamic consequence. Shivering, also a common occurrence during TH induction, can be controlled via routine paralytic use or adequate sedation and the administration of medications such as meperidine. Platelet dysfunction and coagulopathy occur with cooling, and careful attention should be given to clinical evidence of bleeding during the TH period. Electrolyte derangements have also been observed with TH, most notably hypokalemia and hypomagnesemia, presumably from a "cold diuresis" phenomenon. Most hospital TH protocols routinely require electrolytes to be checked every 6 or 8 hours during the TH period to address this issue. Finally, temperature reduction likely attenuates immune function and therefore TH patients may be at increased risk for infectious complications, although the magnitude of this risk is unclear. Potential adverse effects from hypothermia are summarized in Table 49.4.

Practical Issues of Therapeutic Hypothermia

TH induction should begin within 4 to 6 hours after restoration of circulation (ideally as soon as possible), with the goal of achieving target temperature quickly. Generally, this can be achieved within several hours using currently available cooling methodology or adjunctive use of cooled intravenous fluids. Echocardiographic investigations have confirmed that the bolus administration of 1 to 2 liters of cold saline is safe in the postarrest population and can be useful to accelerate the TH process. A noncommercial Internet resource page housing TH-related protocol content can be found at www.med.upenn.edu/resuscitation/hypothermia (accessed August 13, 2012).

Once target temperature is achieved, this temperature can be maintained via the use of a commercial thermostatically controlled cooling device or the careful use of external cold pack/ice application, although the latter is discouraged because overcooling is a sizable risk. During the entire TH process, core temperature should be monitored continuously, preferably via bladder probe or pulmonary artery catheter. Esophageal or rectal temperature monitoring is also considered acceptable, but tympanic temperature is unreliable because of peripheral vasoconstriction during cooling. Risk of life-threatening arrhythmia increases markedly if a patient's temperature falls below 30.0° C, and therefore overcooling should be carefully avoided. Generally most TH patients are both sedated and paralyzed during post-resuscitation care, with standard attention to mechanical ventilation.

Prognosis of postarrest patients had been guided by the landmark 1985 study by Levy and coauthors who reported on the value of serial neurologic examinations on the prognosis of patients who had suffered hypoxic-ischemic coma after cardiac arrest. Because use of TH both confounds the neurologic examination (during TH) and changes the prognosis for a neurologic recovery, the results of the traditional serial neurologic examination to guide prognosis are obsolete in patients treated with TH.

Prognostication of postarrest patients, regardless of TH use, is difficult given current tools at the critical care physician's disposal—clinical features such as gag reflex or papillary responses are considered highly unreliable during the first few days after initial resuscitation. Indeed, the American Academy of Neurology developed a consensus statement on postarrest evaluation in 2006, stating that clinical examination is unable to provide prognostic information in the initial 72 hours post-resuscitation. A variety of studies have evaluated serologic markers, brain computed tomography evaluation, bispectral index monitoring, and other techniques, but not one has emerged as a clinically useful predictor of survival or neurologic outcomes (see Chapter 69).



Content related to resuscitation training and an annotated bibliography can be found at www.expertconsult.com.

Resuscitation Training

There are a variety of reasons underpinning the aforementioned variable quality of CPR performed in hospitals. The level of rescuer training is important; one investigation suggested that survival from in-hospital SCA increases when the first staff member to find the patient has ACLS training. Training and preparation for cardiac arrest events are hampered, however, by the infrequent occurrence of these events and the inadequate frequency of ACLS training and recertification. As evidence, a survey study of Canadian internal medicine residents revealed that they did not feel prepared to act as cardiac arrest team leaders and that they perceived a marked lack of supervision during resuscitation care delivery, especially during nights and weekends (not coincidently, both of these time periods have been found to have worse outcomes for in-hospital SCA compared to those occurring during dayshift nonweekend days). Formal ACLS training is necessary, but an additional problem is that skill retention falls precipitously between certification and subsequent refresher courses. To address these issues, additional skill-based training, real-time feedback, and debriefing have been proposed and investigated.

Although ACLS training imparts the knowledge of how to perform cardiac arrest resuscitation, these courses do not adequately prepare medical personnel with the necessary practical and teamwork skills to perform efficient resuscitation care when required. As evidence, medical personnel often lack comfort in relatively simple issues involved in cardiac arrest resuscitation such as proper placement of defibrillation pads, appropriate CPR quality parameters, and using correct defibrillator energy settings. Also, ACLS certification especially fails when it comes to preparing personnel to serve as team leaders and team members during resuscitation events.

SIMULATION STUDIES OF RESUSCITATION CARE

Increasingly realistic simulation laboratories present an excellent platform to improve resuscitation education. Simulation training has been shown to improve adherence to ACLS guidelines during actual cardiac arrest resuscitation. Additionally, ACLS training sessions in simulation laboratories not only improve resuscitation skills but also appear to minimize skill decay over time. Multiple studies have shown that resident physicians trained by a series of four 2-hour simulator practice sessions improved their ACLS skills and retained their skills for 14 months. Ideally, simulator training should be performed more than once a year. Simulator training should include physicians as well as nurses and other staff involved in cardiac arrest resuscitations, as team interactions across disciplines are an important aspect of resuscitation care.

DEBRIEFING

Focused debriefing following resuscitation care offers promise as a teaching tool, especially with the introduction of CPR quality sensing and recording technology. This technology allows debriefing to cover every aspect of the resuscitation from CPR to ACLS algorithms. Debriefing improves guideline adherence and initial patient outcomes in both simulation laboratory and actual patient resuscitations, but the combination of debriefing with real-time audiovisual feedback creates greater improvements than either method alone. Future work will be required to develop debriefing modalities that are efficient and practical for widespread use.

RESUSCITATION TEAM LEADERSHIP/HUMAN FACTORS

Team leadership represents a complex, difficult-to-teach skill set, yet it plays a large role in the quality of cardiac arrest resuscitation care. Leadership encompasses topics such as task and information distribution as well as conflict management. In simulation studies, effective resuscitation

team leadership has correlated with successful resuscitation. Specifically, high-quality team leaders decrease the amount of time resuscitation teams need to provide basic life support and defibrillation.

Other human factors play important roles in resuscitation care, such as familiarity with resuscitation equipment (defibrillators, airway and suction devices, etc.), ability to arrive at the bedside of an SCA patient and self-assemble into a resuscitation team, and communication skills among team members. These human factors have been inadequately studied in the context of cardiac arrest, and it is likely that the simulation laboratory will provide additional opportunities for improvement in these areas.

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CHAPTER 50

Chest Pain and Myocardial Ischemia

Mitul B. Kadakia ■ Daniel M. Kolansky

Evaluation of chest pain and recognition of myocardial ischemia in patients in intensive care units (ICUs) are essential skills of intensivists. Myocardial ischemia and infarction significantly increase the morbidity and mortality of ICU patients. However, effective interventions have been developed to treat myocardial ischemia and infarction. It is critical to have an understanding of how to provide prompt and appropriate treatment for this condition to effectively care for ICU patients. This chapter describes the approach to the patient with chest pain, the differential diagnosis of chest pain in the ICU, and the optimal treatment for acute coronary syndromes, with particular attention to specific issues that may arise in the ICU setting.

Pathophysiology of Myocardial Ischemia and Acute Coronary Syndromes

Myocardial ischemia and infarction result when myocardial oxygen supply is inadequate to meet myocardial oxygen demand. Myocardial oxygen supply is dependent on available oxygen, the oxygen-carrying capacity of the blood, and the perfusion pressure of and resistance to coronary blood flow. The latter is largely dependent on patency of the coronary arteries. Any fixed stenosis (≥ 70% of lumen) in an epicardial vessel may limit this augmentation of myocardial blood flow, upsetting the normal supply-demand balance and precipitating ischemia. Furthermore, oxygen-carrying capacity may be reduced as a consequence of hypoxemia or anemia, both of which can impair myocardial oxygen supply. Myocardial oxygen demand is dependent on heart rate, contractility, and wall stress. In the ICU patient, fever, pain, and endogenous or exogenous catecholamines promote tachycardia, increased myocardial contractility, and the generation of higher systolic wall tension, all of which increase myocardial oxygen demand.

In the postoperative patient, this oxygen supply may be also diminished as a result of intraoperative blood loss or iatrogenic hypotension. Like critical illness, recovery from major trauma or surgical interventions places extra demands on the myocardium by increasing total-body minute oxygen consumption (see Chapter 8). Finally, oxygen supply-demand balance may also be offset by pharmacologic interventions. For example, vasopressors and inotropic agents may cause tachycardia and augment myocardial contractility, thus increasing myocardial oxygen demand.

The pathophysiology of supply-demand mismatch leading to myocardial ischemia differs from that of acute coronary syndrome (ACS). The anatomic basis for most cases of ACS is the acute fissuring and rupture of an atherosclerotic plaque in an epicardial coronary artery with formation of superimposed thrombus. Plaques that rupture tend to have a thin fibrous coat over a central collection of foam cells, lipid, and necrotic debris. The vulnerable plaque typically ruptures near its junction with normal endothelium, and this exposes collagen and atheromatous material, which, in turn, leads to thrombosis.

The triggers of acute plaque rupture are not fully defined. Most likely, acute hemodynamic stress is the trigger, but acute and chronic endothelial inflammation may also play a role. There

is a circadian variation in the occurrence of all acute cardiovascular events, including myocardial infarction (MI), sudden death, and stroke, with their peak frequency in the first 2 hours after awakening. On arising and assuming an upright posture there are a variety of acute circulatory adjustments, including the release of catecholamines, which results in increased cardiovascular tone and hemodynamic stress. In addition, in these hours there is an increase in blood viscosity and platelet aggregation. Beta-blocker therapy eliminates the higher morning incidence of acute cardiovascular events, which suggests that catecholamine release and hemodynamic stress are important causative events.

The extent of the thrombotic reaction dictates the clinical course and subsequent clinical syndrome. The plaque rupture and superimposed thrombus formation can be transient with resolution via the body's own antithrombotic mechanisms before any permanent myocardial damage. In addition, a variety of vasoactive mediators are released from the endothelial wall that can cause vasospasm and transient complete occlusion. This leads to a syndrome of unstable angina (UA). If the injury is persistent but causes partial occlusion of the vessel, it is classified as non-ST-elevation myocardial infarction (NSTEMI). If the injury is severe and deep, the thrombotic reaction may lead to total occlusion of a coronary artery. This is classified as ST-elevation myocardial infarction (STEMI). The management of these syndromes is separated based on whether the patient is experiencing UA/NSTEMI or STEMI.

Causes of Chest Pain

The differential diagnosis of chest pain in the ICU patient is extensive and includes a number of cardiovascular and noncardiovascular causes (Table 50.1). Esophageal pain shares some features with classic angina; it is typically retrosternal and frequently relieved with nitroglycerin. Reflux pain is often burning in nature, aggravated by lying down, and related to eating. Pain aggravated by movement or by palpation of the affected area is likely to be due to musculoskeletal causes. The description of chest pain may be most helpful in differentiating other cardiopulmonary causes. For instance, the chest pain of pericarditis is typically sharp and pleuritic, relieved by leaning forward. The chest pain of aortic dissection is typically "tearing" in quality, reaches maximal intensity instantaneously, and radiates to the back or flanks. The chest pain of pulmonary embolism, when present, is more often sharp and associated with dyspnea, hypoxemia, or hemoptysis in the absence of other signs of left-sided heart failure. Pneumothorax pain is usually sharp, sudden, and accompanied by dyspnea. Frequently, many patients are admitted to the hospital with a diagnosis of "rule out MI" and are discharged after a cardiac enzyme evaluation is negative and a stress test is normal. These patients have a great deal of uncertainty regarding the actual cause of their chest discomfort, and further evaluation and intervention are essential in their postdischarge care.

Clinical Presentation of Angina and Chest Pain

SYMPTOMS

Recognition and treatment of coronary ischemia in the ICU are important. Ischemia may occur spontaneously or, more often, may occur in the setting of precipitants such as anemia, fever, or postoperative stress. Typical angina may range from a minor discomfort to severe pain. The discomfort is often described as pressure, heaviness, or indigestion. If "pain" is present, it is frequently described as crushing, squeezing, or burning. Classically, angina is located substernally and radiates to the left arm, neck, or jaw. Superficial discomfort is less likely to be caused by myocardial ischemia. Moreover, the chest discomfort of myocardial ischemia does not begin suddenly at maximal intensity but rather crescendos in intensity.

TABLE 50.1 ■ **Causes of Chest Pain in the Intensive Care Unit**

Cardiovascular	Angina
	Acute coronary syndrome/myocardial infarction
	Aortic dissection
	Congestive heart failure
	Pericarditis
Pulmonary	Pulmonary embolism with/without pulmonary Infarction
	Pneumothorax
	Pneumonia
	Pulmonary hypertension
	Pleurisy/pleuritis
	Tracheobronchitis
	Chest tubes
Gastrointestinal	Esophageal reflux
	Esophageal spasm
	Peptic ulcer disease
	Gallbladder disease
	Pancreatitis
	Hepatic capsular distention
	Subdiaphragmatic abscess
Musculoskeletal	Costochondritis
	Arthritis
	Postcardiopulmonary resuscitation (CPR) trauma
	Postoperative incisional or other related pain
	Cervical spine disease
Infectious	Herpes zoster
Psychological	Anxiety
	Panic disorder

Three different anginal syndromes are recognized. *Provocable* angina generally results from transient changes in myocardial supply and demand balance in the setting of a stable, flow-limiting atherosclerotic plaque. *Unstable* angina differs anatomically from provocable angina. It results from rupture of a previously stable plaque with a superimposed thrombus. A significant proportion of patients with unstable angina can progress to acute myocardial infarction, reflecting complete occlusion of a coronary artery. *Variant*, or *Prinzmetal's*, angina, attributed to coronary vasospasm, is neither provocable nor due to plaque rupture and generally occurs at rest.

Although chest discomfort remains the most common complaint of patients with cardiac ischemia, certain *associated symptoms* often support the diagnosis. Patients frequently experience *dyspnea* as a result of increased interstitial pulmonary edema and *diaphoresis* resulting from autonomic instability. *Nausea* and *vomiting* caused by gastric dilatation may ensue as a consequence of cardiac sensory receptor stimulation. *Dizziness* or *syncope* may accompany ischemia or infarction, typically either vasovagally mediated or the result of tachyarrhythmia or bradyarrhythmia.

Symptoms of ischemia or myocardial infarction may be difficult to discern in the critically ill patient because of comorbid illnesses and sedating medications. Even when patients have the capacity to communicate, nearly 20% of those with acute myocardial ischemia or infarction will not develop chest discomfort. In this case, ischemia is "silent"—that is, it manifests only as objective signs in the absence of patient awareness. Recognition of ischemia in the ICU therefore

requires careful scrutiny of hemodynamics, targeted physical examinations, and careful review of electrocardiographic (ECG) changes from baseline.

PHYSICAL FINDINGS

Physical signs of myocardial ischemia are frequently nonspecific in the critically ill patient. Vital sign abnormalities can suggest a perturbation in cardiac function. When tachycardia is present and accompanied by a thready pulse, compromised cardiac output must be suspected. Alternatively, bradycardia may be seen because of excessive vagal tone or sinoatrial or atrioventricular nodal ischemia; in association with poor peripheral perfusion, this condition suggests right ventricular ischemia or infarction. Hypertension may accompany ischemia, secondary to excessive catecholamine release, whereas relative hypotension may also occur on the basis of impaired cardiac output.

After evaluation of vital signs, physical examination should include a thorough cardiovascular, pulmonary, and extremity exam. Examination of the heart may reveal a new S3 or S4 gallop from acute systolic or diastolic dysfunction. Precordial examination may reveal an ectopic impulse from a bulging akinetic myocardial segment. There may be a murmur of mitral regurgitation caused by ischemia of the papillary muscle. Jugular venous pressure may be elevated if right ventricular failure is present. When ischemia is accompanied by left ventricular heart failure, auscultation of the lungs may reveal crackles, resulting from opening of fluid-filled alveoli, or wheezes, resulting from reflex bronchoconstriction. Peripheral signs of ischemia include diaphoresis with cool, clammy skin, ashen skin caused by peripheral vasoconstriction or cyanosis, slow capillary filling, and *livedo reticularis* resulting from poor cardiac output.

Diagnostic Evaluation

ELECTROCARDIOGRAM (ECG)

The electrocardiogram (ECG) is a crucial source of data in the evaluation of chest pain. It should be obtained as soon as possible after presentation in patients with chest discomfort. In addition, it should be obtained in the ICU patient routinely, particularly if there are unexplained changes in vital signs or physical signs, such as tachypnea, hypotension, or tachycardia. Either transient ischemia or frank myocardial infarction may be identified. The key changes of myocardial ischemia or infarction on the ECG are repolarization abnormalities, arrhythmias, or conduction blocks.

Repolarization Abnormalities

Most commonly, myocardial ischemia is accompanied by changes in the T waves or ST segments on the standard 12-lead ECG. These include transient T-wave inversion or ST-segment depression. Right coronary artery ischemia is best visualized in leads II, III, and aVF; circumflex artery ischemia in leads I, aVL, V_5, and V_6; and left anterior descending (LAD) artery ischemia in the precordial leads, V_1 to V_4. Leads V_1 and V_2 may also reflect posterior wall ischemia or infarction by recording electrical forces opposite in direction to the forces of anterior ischemia. This is attributable to ischemia of the right coronary artery or the left circumflex artery (whichever is dominant).

The classic ECG manifestation of ischemia is downward displacement of the ST segment (Figure 50.1). Horizontal and downward-sloping ST segments are generally more specific than upsloping ST segments. Although less specific, flattening of the ST segment with increased angulation at the ST-segment/T-wave junction also suggests ischemia. With resolution of ischemia, ST segments typically return to baseline. When ST segments remain depressed, subendocardial myocardial infarction should be suspected. ST-segment elevation is consistent with acute transmural myocardial infarction and is often followed by T-wave inversion and the appearance of



Figure 50.1 Twelve-lead electrocardiogram (ECG) from a 76-year-old diabetic, hypertensive man with excellent exercise tolerance, who developed asymptomatic ECG changes on the first postoperative day after total hip replacement. He ruled in for myocardial infarction and developed heart failure; cardiac catheterization revealed left main and three-vessel disease. Note ST-segment depression in leads I, II, III, aVF, and V_3 through V_6, with reciprocal ST-segment elevation in lead aVR.

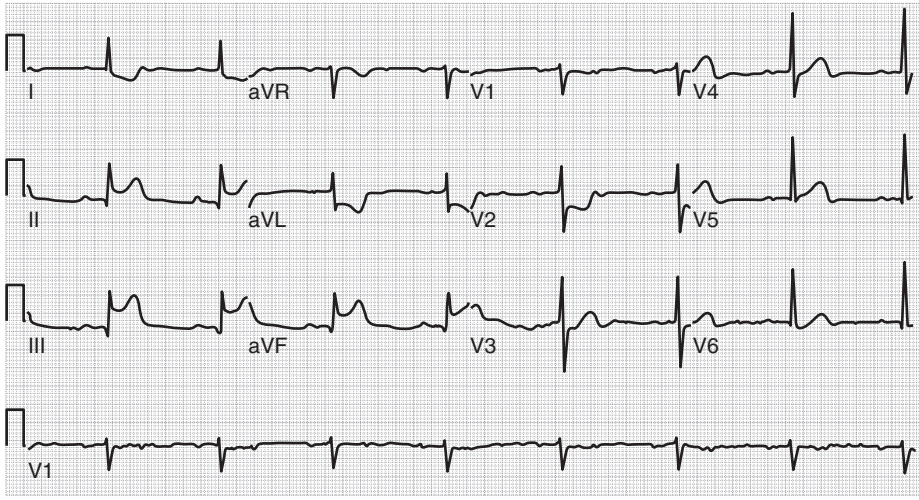
Q waves (Figure 50.2*A*). A new left bundle branch block (LBBB) is felt to be equivalent to an ST-segment elevation infarction as it may represent complete occlusion of the LAD prior to septal branches that perfuse the left bundle branch. Less often, ST-segment elevation reflects transient myocardial ischemia secondary to vasospasm (Prinzmetal's angina). Diffuse, widespread ST elevation may be secondary to pericarditis.

Interpretation of T-wave changes in the absence of ST-segment changes is more difficult, owing to lack of specificity. T-wave inversion is most suggestive of ischemia when deep and symmetric in several leads; less specific are T waves that invert asymmetrically, with a gentle downslope and a rapid upslope. Such T-wave morphologies are typical of repolarization abnormalities seen in association with ventricular hypertrophy or bundle branch block. In patients whose baseline ECG demonstrates inverted T waves, ischemia may result in pseudonormalization of T waves to the upright position.

In the ICU, postural adjustments, hyperventilation, neurologic events (e.g., subarachnoid hemorrhage), and anxiety can produce T-wave changes identical to those precipitated by ischemia. A number of pharmacologic agents often used in the ICU may also produce T-wave changes, including digitalis, antiarrhythmic drugs, sympathomimetic and sympatholytic agents, tricyclic antidepressants, barbiturates, lithium, and insulin. A variety of reversible extracardiac illnesses frequently seen in the ICU have also been implicated in T-wave changes, including allergic reactions, hemorrhage, viral infections, hypothyroidism or hyperthyroidism, adrenal insufficiency, hypokalemia, strokes, pulmonary embolism, and intra-abdominal diseases, such as acute pancreatitis or acute cholecystitis.

Arrhythmias (see Chapters 33 and 34 for more details)

Arrhythmias may be additional ECG manifestations of myocardial ischemia or infarction, although they may also occur as a manifestation of structural heart disease (hypertension, left atrial abnormalities, etc.). These can include atrial arrhythmias (atrial tachycardia, atrial fibrillation,



A

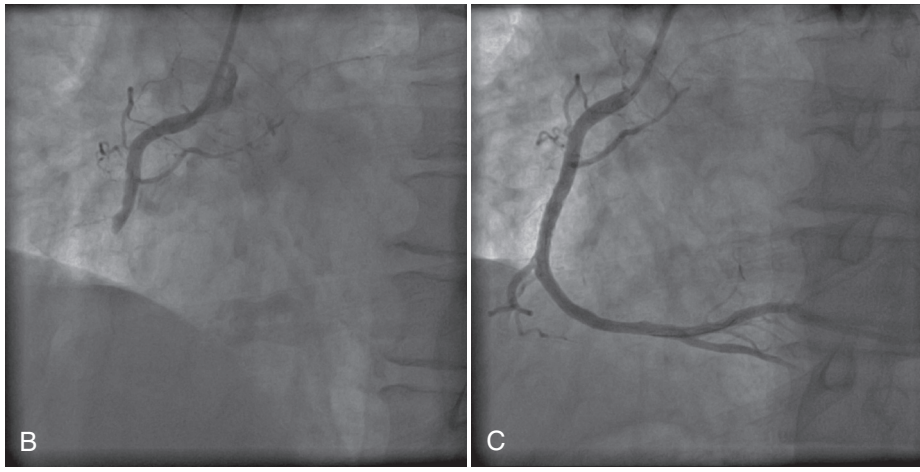


Figure 50.2 **A,** Twelve-lead electrocardiogram (ECG) from a 51-year-old man with a history of hypertension and hyperlipidemia who presented with 2 hours of chest pain. ECG revealed ST-elevation myocardial infarction, and he was referred for emergent cardiac catheterization. Note ST elevations in leads II, III, and avF with reciprocal ST-segment depression in leads I and avL. There is also an R-wave in V1 and V2 with ST-segment depression. This is consistent with an inferoposterior myocardial infarction. **B,** Cardiac catheterization revealed a completely occluded right coronary artery. Successful percutaneous coronary intervention was performed on this lesion with a good outcome for the patient. **C,** Following percutaneous coronary intervention and stent placement, the patient achieved complete reperfusion of the infarcted territory and his symptoms resolved.

and atrial flutter), sinus tachycardia, and ventricular tachycardia/fibrillation. Conduction blocks ranging from first-degree atrioventricular (AV) block to complete heart block can also be seen.

CHEST RADIOGRAPHY

In the setting of myocardial ischemia, chest radiographs frequently demonstrate evidence of interstitial or alveolar edema. When it appears in an interstitial pattern, edema manifests as

haziness among pulmonary vascular markings, owing to pulmonary venous engorgement as well as peribronchial cuffing. This is accompanied by thickening of interlobular septa with engorged lymphatic vessels, known as Kerley B lines, which appear as short, horizontal, linear densities at the lung periphery. If interstitial fluid accumulates rapidly, it may flood alveoli, resulting in confluent opacification, usually in a perihilar or "batwing" distribution. Unilateral or bilateral pleural effusions may also accompany acute ischemic cardiac failure.

CARDIAC ENZYMES

Myocardial injury results in the release of a variety of intracellular biochemical markers. The most commonly measured of these include creatine kinase (CK), its dimeric isoform CK-MB (isoenzyme of creatine kinase with muscle and brain subunits), and troponins I and T (Table 50.2). Typically, postinfarction CK and CK-MB appear within 4 to 6 hours and peak within 18 to 24 hours. Both remain elevated for 48 to 72 hours following infarction, but, as a result of faster clearance, CK-MB usually returns to baseline before total CK. Measurement of CK and its isoenzymes is very sensitive, but trace amounts of CK-MB are also found in a number of other tissues, so care must be taken in interpreting rises in CK-MB after surgery or trauma.

Cardiac *troponins* are structural proteins found in cardiac muscle that regulate calcium and the interaction with actin and myosin. During cellular injury, both troponin T and I are released from damaged cells. Troponins appear at 2 to 6 hours after symptom onset, peak at 15 to 20 hours, and remain elevated 5 to 7 days postinfarction. Unlike CK, troponins T and I are not usually detectable in serum in the absence of myocardial injury. Because of the rapidity of the immunoassay for troponin I and its specificity, measurement of this marker has become the test of choice for perioperative and ICU patients. In both unstable angina and acute MI, troponins are also important prognostic indicators and identify patients at increased risk of further cardiac events.

It is important to note that although troponins are very specific to myocardial tissue, troponin elevations can result from causes of myocardial damage other than acute coronary syndromes. These causes can include congestive heart failure, pericarditis, trauma, sepsis, pulmonary embolism, and anemia from acute blood loss. Moreover, as troponins are renally cleared, renal failure can lead to elevated serum troponin levels. These mild and at times persistent elevations of serum troponin levels may require evaluation but often do not require additional testing or intervention.

Risk Stratification

A number of measures are used to assess the significance of myocardial ischemia in the ICU setting and to predict the risk of adverse cardiac outcomes.

THROMBOLYSIS IN MYOCARDIAL INFARCTION (TIMI) RISK SCORE

The Thrombolysis in Myocardial Infarction (TIMI) risk score is a well-validated scoring system used to predict the risk of death, myocardial infarction, or urgent revascularization in patients with UA/NSTEMI. It is composed of seven independent risk factors: (1) age greater than or equal to 65 years, (2) three or more risk factors for coronary artery disease, (3) history of known coronary artery disease (> 50% stenosis), (4) aspirin use within the prior week, (5) two or more anginal episodes in the prior 24 hours, (6) ST deviation greater than 0.5 mm, and (7) positive cardiac biomarkers. Those with zero or one risk factor had a 4.7% risk, whereas those with seven risk factors had a 40.9% risk. The TIMI risk score is also helpful for deciding whether a patient should undergo a conservative or invasive strategy. Those with intermediate (TIMI score 3 to 4) or high (TIMI score 5 to 7) risk scores have improved outcomes with an invasive strategy. At times this score may be a useful tool for evaluating patients in the ICU who have presented with unstable angina.

TABLE 50.2 ■ **Assessment and Management of Chest Pain in the Intensive Care Unit**

History	Character, timing, radiation of pain
	Associated symptoms
	Cardiac risk factors
Physical Exam	Vital signs
	Focused cardiac and pulmonary examination
	Signs of congestive heart failure
Diagnostic Evaluation	ECG (ST-T new wave changes consistent with ischemia/infarction; Q waves; arrhythmias)
	Cardiac biomarkers (troponin, CK, CK-MB)
Risk Stratification	TIMI risk score
	Echocardiography
Contributing Causes	Consider precipitants for ischemia other than acute coronary syndrome
	—Sepsis
	—Hypovolemia
	—Trauma
	—Anemia
	—Stress from postoperative state
Medical Therapy	Anti-ischemic therapy
	—Oxygen
	—Analgesia
	—Beta-blockers
	—Nitrates
	Antiplatelet therapy
	—Aspirin
	—Thienopyridines (i.e., clopidogrel)
	—Glycoprotein IIb/IIIa inhibitors
	Anticoagulant therapy
	—Heparin, low-molecular-weight heparin
	Statins
	ACE inhibitors
Invasive Therapy	STEMI
	—Prompt angioplasty/PCI
	—Thrombolytics if PCI not available
	NSTEMI/UA
	—Consider invasive approach within 24–48 hours

ACE inhibitor, angiotensin-converting enzyme inhibitor; CK, creatine kinase; CK-MB, creatine kinase-MB fraction; NSTEMI/UA, non-ST-elevation myocardial infarction/unstable angina; PCI; percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIMI risk score, see text for details.

ECHOCARDIOGRAPHY

Left ventricular systolic dysfunction is an important prognostic indicator in ischemic heart disease. Echocardiography, by virtue of its capacity to assess global and regional ventricular function, has become a useful bedside tool in the evaluation of patients with coronary artery disease (CAD). Regional function analysis includes an assessment of both wall thickening and motion toward the left ventricular center. Segmental abnormalities of wall thickening or motion that are

coexisting with areas of normally contractile myocardium are highly suggestive of ischemic heart disease. Areas of thinned and akinetic myocardium suggest the presence of scarred or chronically hypoperfused myocardium. Echocardiography can also reveal new valvular disease that may result from ischemia, such as mitral regurgitation. In conjunction with either exercise or dobutamine-enhanced contractility, echocardiography has a predictive value for detecting coronary artery disease approaching that of traditional single-photon emission computed tomography (SPECT) perfusion imaging.

NUCLEAR IMAGING

SPECT myocardial perfusion imaging with either thallium-201 or technetium-99m is very sensitive for the diagnosis of coronary artery disease. When thallium-201 or technetium-99m is injected intravenously, it accumulates in well-perfused myocardium. SPECT can be performed in conjunction with exercise or dipyridamole, adenosine, or dobutamine infusion to identify zones of myocardium where augmentation of coronary blood flow is limited by arterial stenosis. In the presence of flow-limiting coronary arterial stenosis, planar or tomographic images demonstrate a regional decrease in radiotracer uptake. Ischemia is represented by reversibility of a regional defect on rest images, whereas persistence of the perfusion defect implies the presence of scar. In the ICU setting, injection of radiotracer during or after suspected ischemia identifies both the location and severity of disease, thus offering unique prognostic information.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) of the heart is emerging as an important tool for evaluating myocardial function and assessing myocardial viability. Delayed enhancement on imaging can indicate areas of scarred and nonviable myocardium, which may be important in decision making regarding coronary revascularization. Additionally, stress-testing protocols have been developed with MRI imaging but are not yet in widespread use.

CORONARY CT ANGIOGRAPHY

Coronary computed tomography (CT) angiography is a non-invasive modality through which epicardial coronary artery stenosis can be identified. This test has a high sensitivity and specificity for detecting significant epicardial coronary stenoses (> 70%). However, it does not provide a means to assess whether a given lesion causes ischemia. Additionally, there is no ability to intervene on a significant stenosis during a CT angiogram. The role of such angiography in the ICU setting is limited, but it can be helpful in excluding the presence of CAD in specific settings.

Management of Ischemia and Infarction

The goals of therapy for suspected myocardial ischemia are (1) anti-ischemic therapy to restore the oxygen supply-demand balance, (2) counteract the prothrombotic factors contributing to plaque rupture and thrombosis, and (3) reperfuse the occluded vessel.

ANTI-ISCHEMIC THERAPY

Oxygen

Supplemental oxygen administration should be given to all patients whose oxygen saturation is < 90% or in respiratory distress. This can help increase myocardial oxygen supply and reduce

ischemia. In patients with normal oxygen saturation, supplemental oxygen may be harmful and is not recommended.

Bed Rest

Patients should be placed in a calm, quiet atmosphere with limited to no activity to minimize myocardial oxygen demand from increased sympathetic tone resulting from exertion, anxiety, or emotional stress.

Analgesia

Effective analgesia is an important component of reducing myocardial oxygen demand. Pain can lead to increased sympathetic tone and tachycardia, both of which increase oxygen demand. Opioids, such as morphine sulfate, fentanyl, and meperidine, are especially useful analgesics. In addition to acting as an analgesic, morphine has venodilatory effects that may improve hemodynamics by reducing preload. Morphine (2 to 5 mg intravenously [IV] every 10 to 30 minutes as needed [prn]) or fentanyl (25 to 50 mcg IV every 5 to 30 minutes as needed) is considered first-line therapy, except in patients with documented allergies. In patients with inferior ischemia, meperidine may be particularly helpful as a result of its vagolytic properties. With cumulative doses of opioids, care must be taken to avoid respiratory depression, which may precipitate hypoxemia and exacerbate ischemia.

NITRATES

Initial therapy for suspected ischemia should include nitrates (see Table 50.2). In addition to venodilation, which results in reduced preload and thus lowered end-diastolic pressures, nitrates cause arteriolar dilation, which reduces systemic arterial pressure and ventricular afterload. They can also reverse coronary arterial spasm, generating an early increase in myocardial blood flow. Because of their effect on preload, nitrates are especially valuable in patients with elevated left-sided filling pressures resulting in congestive heart failure (Chapter 52). The most significant adverse effect of nitroglycerin is hypotension, which can exacerbate myocardial ischemia. Therefore, nitrates should be avoided in the setting of profound hemodynamic compromise or severe aortic stenosis. Nitrates should also be avoided in patients with right ventricular infarction as a sudden drop in preload can precipitate severe hypotension.

Sublingual nitroglycerin may be administered with close monitoring of hemodynamics. If angina or ECG abnormalities persist, additional doses of sublingual nitroglycerin may be given 5 minutes apart, as long as they are tolerated hemodynamically. For more precise control, continuous IV nitroglycerin may be initiated and titrated until symptoms are controlled or until mean arterial pressure falls by at least 10% in normotensive patients or by at least 25% in hypertensive patients. Nitrate tolerance may result from prolonged IV infusion, resulting in recurrence of symptoms or relative hypertension. Long-term nitrate therapy can be delivered effectively with oral isosorbide dinitrate or mononitrate, or with nitroglycerin paste or patches, allowing a nitrate-free period each day to avoid tolerance. Nitrate-induced headaches are a common side effect, but they are usually mild, can be managed with analgesics, and subside within a week.

Beta-Blockers

Beta-blockers are a cornerstone of therapy for acute myocardial ischemia (see Table 50.2). In addition to their anti-ischemic properties, they are efficacious in reducing mortality acutely in the setting of acute myocardial infarction. By reducing heart rate, blood pressure, and contractility, beta-blockers effectively reduce myocardial oxygen demand. Additionally, the negative chronotropic effect of beta blockade prolongs diastole with concomitant augmentation of

coronary blood flow and myocardial oxygen supply. All patients with ischemia, especially those with reflex tachycardia or coexisting hypertension, are potential candidates for beta-blockers. If the patient is having ongoing chest pain or ischemia, IV beta-blockade can be used followed by oral beta-blockade.

Important contraindications to beta-blockers include severe aortic stenosis, bradycardia, atrioventricular conduction defects, and reactive airway disease. Bronchospasm may be minimized with the use of $beta_1$-cardioselective drugs, such as atenolol, esmolol, or metoprolol. At higher doses, these agents become less selective and may reduce expiratory flows by blocking airway $beta_1$ receptors. Intravenous beta-blockade should be avoided in patients with heart failure and left ventricular dysfunction; however, there is a mortality benefit for chronic oral beta-blockade in this group of patients (Chapter 52).

Some beta-blockers, such as propranolol, metoprolol, and labetalol, have *membrane-stabilizing* or quinidine-like activity. Such type I antiarrhythmic effects are unrelated to their beta-blocking properties. Their overall effect is to prolong the effective refractory period relative to the action potential duration, which may benefit patients prone to ischemia-induced ventricular tachyarrhythmias. *Metoprolol* is an appropriate first-choice beta-blocker because of its cardioselectivity and membrane-stabilizing activity.

CALCIUM CHANNEL BLOCKERS

Calcium channel antagonists are also effective antianginal agents and should be considered second-line therapy for myocardial ischemia in the ICU. Because of the mortality benefit of beta-blockers, calcium channel blockers should only be used in patients in whom there is a contraindication to beta-blockers or in patients with recurrent ischemia despite maximal therapy with beta-blockers. A variety of calcium channel blockers are available, and each has a different effect on contractility or atrioventricular conduction (Table 34.3 in Chapter 34). The most commonly used calcium channel blockers are verapamil and diltiazem. Diltiazem has been shown to be harmful in patients with left ventricular dysfunction and should be avoided in this population. Nifedipine, which does not affect heart rate, has been shown to lead to worse outcomes in myocardial infarction when not given with a beta-blocker.

When administered orally, calcium channel blocker therapy should be initiated at low doses and titrated as tolerated. Relative contraindications to calcium channel blockers include severe aortic stenosis, atrioventricular conduction defects, congestive heart failure, and hypotension. Additional drugs often used in the ICU that may interact with calcium antagonists include amiodarone (potentiates atrioventricular conduction defects), cimetidine (increases bioavailability of calcium antagonists), neuromuscular blockers (action potentiated by calcium antagonists), cyclosporine and digoxin (increased plasma levels), quinidine (decreased plasma levels), and phenobarbital and rifampin (decreased hepatic enzyme induction).

ANTIPLATELET AGENTS

Aspirin

Aspirin exerts its beneficial effect through inhibition of cyclooxygenase and hydroperoxidase reactions, thus limiting the production of thromboxane A_2, a potent vasoconstrictor and promoter of platelet aggregation. By doing so, platelet aggregation at the site of thrombus formation is reduced. Aspirin alone reduces the risk of death or myocardial infarction by 50%. If there are no strong contraindications, patients should be given 162 to 325 mg of aspirin immediately (chewed and swallowed or chewed and kept sublingual). Following this initial loading dose, a dose of 75 to 81 mg can be continued for chronic use. Contraindications to aspirin use include allergic reaction, bleeding, or history of a platelet disorder.

Thienopyridines

Clopidogrel is the most commonly used thienopyridine. It inhibits the ability of adenosine diphosphate (ADP) to bind to the P2Y12 component of platelet ADP receptors. This reduces ADP-induced platelet aggregation. Clopidogrel also appears to reduce platelet aggregation and activation by other mediators. The addition of clopidogrel to aspirin in patients with UA/NSTEMI can reduce the risk of death, MI, or stroke by 20% to 30% both in patients who are treated medically as well as those who undergo a percutaneous coronary intervention.

Clopidogrel should be administered as an initial oral loading dose of 300 to 600 mg followed by 75 mg/day. A 600-mg dose is preferred in patients who are undergoing immediate or urgent percutaneous coronary intervention, as it achieves a steady-state level of platelet inhibition in less time than the 300-mg dose (2 hours versus 4 to 6 hours). Contraindications to clopidogrel include allergy to the drug, bleeding, and a history of platelet disorders, such as thrombotic thrombocytopenic purpura (TTP) (Chapter 63).

Many patients have been identified as "nonresponders" or "low responders" to clopidogrel. Clopidogrel is a prodrug and, after intestinal activation, must be converted to its active form by the hepatic CYP2C19 enzyme. Genetic polymorphisms may be present with some patients having reduced CYP2C19 function, leading to interpatient variability in plasma levels of active metabolite and, consequently, effectiveness of platelet inhibition. In addition, a number of medications may also affect clopidogrel metabolism. Assays for genetic screening for polymorphisms and clinical assays for assessment of platelet inhibition are currently available, and their roles in the management of patients requiring antiplatelet agents are being studied.

Compared to clopidogrel, *prasugrel* is a newer thienopyridine that is also an effective agent for clopidogrel nonresponders. This drug does not require conversion by CYP2C19 and has been shown to be effective in patients with acute coronary syndrome undergoing stenting. However, there are increased bleeding risks with prasugrel, and it must be avoided in those with a history of stroke. Another option is *ticagrelor*, a nonthienopyridine ADP inhibitor, which has also been shown to be effective in patients with acute coronary syndrome.

Glycoprotein (GP) IIb/IIIa Inhibitors

GP IIb/IIIa inhibitors act on the final common pathway of platelet aggregation by preventing fibrinogen mediated platelet cross-linking via GP IIb/IIIA receptors. Commonly used GP IIb/IIIa inhibitors include eptifibatide and abciximab. The use of these agents should be considered in high-risk patients (TIMI risk score 5 to 7, substantial troponin elevations, recurrent chest discomfort despite maximal medical therapy, hemodynamic instability, or significant ECG changes) as adjunctive antiplatelet therapy. This applies in patients who are being managed invasively as well as in those managed conservatively. Care must be taken with these agents given the increased risk of bleeding.

ANTICOAGULANT THERAPY

Unfractionated Heparin

Unfractionated heparin exerts its antithrombotic effect via activation of antithrombin III, which then inactivates thrombin and factor Xa. This disrupts the coagulation cascade. In combination with aspirin, heparin has been shown to reduce the risk of death or MI when compared to aspirin alone. As such, it has been a key component of ACS therapy. Intravenous heparin is best administered on a weight basis, with a bolus of 60 units/kg, followed by a continuous IV infusion at a rate of 12 units/kg/h. Heparin requirements are variable, and optimal therapeutic benefit with minimization of bleeding complications is best accomplished when the activated partial thromboplastin (PTT) time is maintained at 1.5 to 2 times control. Risks of unfractionated heparin include bleeding and heparin-induced thrombocytopenia (Chapter 45).

Low-Molecular-Weight Heparin

Low-molecular-weight heparins (LMWHs) are an alternative to unfractionated heparin (UFH) in the management of ACS. They work via inhibition of both factor IIa and factor Xa in the coagulation cascade. The advantages of LMWHs are that they can be administered subcutaneously in two daily doses without a need for monitoring of partial thromboplastin time. They provide a more reliable and steady level of anticoagulation. Clinical trials have suggested there may be a benefit to using LMWHs over UFH in patients with ACS. LMWHs should be used with caution in patients with renal dysfunction. Moreover, even in patients with normal renal function, LMWHs have a long therapeutic window and their effect cannot be readily reversed as can the effect of UFH (e.g., by giving protamine). Thus, they may not be ideal in patients who may undergo an invasive strategy and could require reversal of anticoagulation at the time of vascular access or vascular sheath removal.

Direct Thrombin Inhibitors

Direct thrombin inhibitors exert their beneficial effect by inhibiting factor IIa (thrombin). Bivalirudin is the most widely studied and used of this category of agents. Data have suggested that bivalirudin may be as effective as UFH or LMWH with less bleeding, when used as the anticoagulant during percutaneous coronary intervention (PCI) procedures. It may also be used as an alternative anticoagulant during PCI in patients who have a history of heparin-induced thrombocytopenia.

STATINS

Long-term treatment with statins in patients with CAD has an important mortality benefit, and these agents are widely used. In addition, there is also a role for statins in the acute treatment of ACS. Besides their lipid-lowering effects, statins are posited to have pleiotropic anti-inflammatory effects that can be effective in ACS. Clinical trials have demonstrated a reduction in death, MI, and stroke in patients treated early with intensive statin therapy. Atorvastatin 80 mg should be prescribed to all patients with ACS who do not have a major contraindication. This treatment should be continued for at least 30 days after which the dose can be adjusted based on the patient's lipid levels. Statin therapy can cause myositis and rhabdomyolysis and should also be used with caution in patients with liver disease.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITORS

Ventricular remodeling is a term that encompasses all the changes that occur in left ventricular size, shape, and function after an acute MI. Characteristically, the infarcted area of myocardium expands, which may result in progressive LV enlargement and a detrimental effect on both LV function and prognosis. Severe, prolonged ischemia may lead to stunning and reduced contractile function. Reducing LV wall stress early in the course of an acute infarct improves LV function and decreases LV size.

In patients with decreased ejection fraction following myocardial infarction, angiotensin converting enzyme inhibitors (ACE inhibitors) provide an important mortality benefit related to beneficial effects on ventricular remodeling. Though it has not been shown in clinical trials, patients with preserved ejection fraction may also benefit. It is recommended that all patients with ACS be initiated on an ACE inhibitor prior to discharge.

REPERFUSION THERAPY

In addition to medical treatment, coronary reperfusion therapy for patients with acute coronary syndromes has become a cornerstone of treatment in appropriate cases of myocardial infarction.

Generally these patients are identified as having either ST-elevation myocardial infarction (STEMI) or non-ST-elevation infarction (NSTEMI). For patients with STEMI (or acute chest pain with new LBBB), prompt reperfusion with percutaneous coronary intervention (or thrombolytic therapy) is critical. These patients undergo prompt cardiac catheterization and coronary stenting when feasible. PCI has improved outcomes as compared to thrombolytic therapy in such cases. There is also an increased risk of stroke with thrombolytic therapy as compared to PCI. There are still medical treatment facilities where immediate PCI is not available, and thrombolytic therapy may be used.

In addition to patients with obvious STEMI or chest pain with new LBBB, those with persistent chest discomfort despite medical therapy or hemodynamic instability should also be referred for prompt catheterization.

In patients with UA/NSTEMI who are initially stabilized with medical treatment, an invasive approach with cardiac catheterization is warranted during the hospitalization of those who have high-risk features, such as positive troponin or ECG changes. Ideally, this should occur within 24 to 48 hours of presentation. However, in the ICU patient with multiple active medical problems, it may be prudent at times to await the resolution of other active issues before proceeding with catheterization. Thrombolytics have not been shown to have a role in patients without ST-segment elevation and thus are not indicated in patients with UA/NSTEMI.

PREVENTION OF SUDDEN CARDIAC DEATH

As discussed earlier, patients with ACS are at high-risk of ventricular arrhythmias. Those with an ejection fraction of < 35% or with ventricular tachyarrhythmias that persist following reperfusion therapy should be considered for implantable cardioverter-defibrillator (ICD) therapy. Current recommendations suggest that a repeat assessment of ejection fraction should be performed 6 weeks following the initial event. When the ejection fraction remains depressed (< 35%), then an ICD should be placed, as long as there are no other comorbidities that will significantly reduce life expectancy.

Complications of Myocardial Infarction

CARDIOGENIC SHOCK

Although the frequency of cardiogenic shock in acute MI has decreased to 7% compared with 20% in the prethrombolytic era, the mortality remains high at 50% to 60% (see Table 50.2). Shock usually results from extensive loss of myocardial mass and contractile function but may occur with other mechanical complications of infarction. Clinical and hemodynamic assessments are both valuable in risk stratification and for determining the therapeutic approach to patients with shock (see Table 50.2 and Chapter 8). Shock may occur because of relative or absolute hypovolemia, especially in patients with increased vagal tone and peripheral venodilation.

Hemodynamic monitoring is often necessary to optimize volume status, cardiac output, and peripheral oxygen delivery, and it can be an important aspect of the ICU management of such patients. Pulmonary arterial catheterization using a flow-directed (Swan-Ganz) catheter allows rapid measurement of central venous, right ventricular, pulmonary arterial, and pulmonary artery wedge pressure. The latter approximates left ventricular end-diastolic pressure or left atrial pressure, which is often elevated in the setting of ischemia. Additional information can be helpful in specific settings, such as the presence of large V waves on the wedge pressure tracing suggesting mitral regurgitation, possibly the result of ischemic papillary muscle dysfunction or rupture. Measurement of both pulmonary artery wedge pressure and cardiac output is useful in guiding pharmacologic intervention. Right-sided heart catheterization in the setting of myocardial

infarction can also be helpful for recognizing right ventricular infarction and rupture of the ventricular septum.

A number of invasive approaches and support devices are also available in the ICU setting that may play a role in management of cardiogenic shock. Intra-aortic balloon pumps (IABPs) provide a beneficial hemodynamic effect by increasing coronary perfusion in diastole as well as augmenting stroke volume by creating reduced afterload during systole. IABPs are also especially useful with persistent, refractory chest pain and myocardial ischemia. In contrast, inotropic agents augment cardiac output at the expense of increased myocardial oxygen consumption and risk increasing infarct size. Direct restoration of blood flow with coronary angioplasty, within hours of the onset of shock, reduces mortality and should be considered in every patient with extensive infarction and cardiogenic shock (also see Chapter 8). The development of effective LV-assist devices (LVADs) provides an additional approach for patients with refractory shock. Percutaneous devices such as TandemHeart and Impella can be placed in the catheterization laboratory. These are temporary devices though. More permanent LVADs are also available (Chapter 88). These devices are currently used primarily as bridges to cardiac transplantation but can also be used as permanent therapy.

DYSRHYTHMIAS AND CONDUCTION DISTURBANCES

Arrhythmias

Sinus tachycardia, resulting from pain, anxiety, or heart failure, is the most common supraventricular arrhythmia in patients with myocardial ischemia. Sinus bradycardia is usually seen in the setting of inferior ischemia, as a result of the high concentration of vagal efferent nerves in the inferoposterior wall and sinus node. Less frequent supraventricular arrhythmias include atrial tachycardia, atrial flutter, and atrial fibrillation. The underlying causes of these arrhythmias are atrial ischemia and increased left atrial pressure resulting from pump failure, pericarditis, or excess catecholamines.

When these dysrhythmias develop, they should trigger a reevaluation of ventricular function and overall management. Tachycardia increases myocardial oxygen consumption and may increase infarct size. Treatment of atrial arrhythmias depends on the patient's hemodynamics and degree of systolic dysfunction. If a patient in atrial fibrillation or flutter is actively ischemic, hemodynamically unstable, or both, synchronized electrical cardioversion should be performed immediately. If otherwise stable, these patients may be treated first with an atrioventricular nodal blocking agent, such as IV beta-blockers, to slow ventricular response.

Ventricular arrhythmias are more concerning for myocardial ischemia. The most common ventricular arrhythmias are polymorphic ventricular tachycardia (PMVT) and ventricular fibrillation (VF). Monomorphic ventricular tachycardia is unusual as this arrhythmia usually originates from scar rather than areas of active ischemia. Isolated premature ventricular contractions (PVCs) are also common and do not require treatment. Although these are usually of little concern, they may be harbingers of more serious ventricular arrhythmias, such as PMVT or ventricular fibrillation (VF). The treatment of ventricular dysrhythmias is also dictated by patient stability. Patients with unstable VT, PMVT, or VF should be electrically cardioverted immediately. Patients with sustained VT who are not actively ischemic or hemodynamically unstable may be initially treated with IV lidocaine or amiodarone (Chapter 34). The persistence of such serious ventricular dysrhythmias is an ominous prognostic sign and requires additional evaluation and treatment.

Accelerated idioventricular rhythms, usually at rates between 60 and 100, also frequently occur, especially with inferior infarction. In general, this rhythm disturbance is benign, self-limited, and well tolerated and does not usually require treatment.

Conduction Blocks

Conduction block may be another manifestation of myocardial infarction in the ICU. Atrioventricular nodal blockade is most often evident in the presence of *inferior* ischemia or infarction, owing to

excessive vagal tone or to hypoperfusion by means of the atrioventricular nodal branch. First-degree, second-degree (Mobitz type I), or third-degree block may occur (Chapter 33). Conduction block from inferior ischemia is self-limited and usually does not portend a poorer prognosis; transvenous pacing is warranted if a patient develops hemodynamic instability, becomes symptomatic, or has bradycardia-dependent ventricular arrhythmias that accompany inferior ischemia. Normal conduction often returns after successful reperfusion and a permanent pacemaker is rarely needed. Right bundle branch block or left posterior hemiblock may also occur in this setting, because branches from the posterior descending artery perfuse both the proximal third of the right bundle and the left posterior fascicle.

In cases of *anterior* ischemia or infarction, conduction block carries a poorer prognosis. The left anterior descending artery supplies blood to the distal right bundle, the main left bundle, and the left anterior fascicle. Block resulting from hypoperfusion in the left anterior descending arterial distribution is more typically infranodal than in inferior ischemia and is manifest as Mobitz type II second-degree heart block, left or right bundle branch block, or third-degree heart block. Transvenous pacing is usually warranted under these circumstances. As described previously, a new left bundle branch block is also concerning for acute total occlusion of the proximal LAD and immediate reperfusion is warranted.

RIGHT VENTRICULAR INFARCTION

Right ventricular (RV) infarction is a common but frequently unrecognized complication that can lead to both decreased RV diastolic compliance and systolic dysfunction. The clinical triad of elevated jugular venous pressure, hypotension, and clear lung fields in the setting of acute inferior ECG changes strongly suggest this diagnosis. Other evidence of RV infarction includes Kussmaul's sign, tricuspid regurgitation, a right-sided S3 gallop, exaggerated pulsus paradoxus, and ST-segment elevation in V_1 and the right-sided leads on the ECG. RV infarction substantially increases the risk of death and complications, including AV block, cardiogenic shock, and ventricular fibrillation. The primary treatment is vigorous volume expansion to raise the LV filling pressure and restore LV stroke volume. Most patients have improvement in RV function in 2 to 3 days after the acute MI.

PAPILLARY MUSCLE DYSFUNCTION AND RUPTURE

Severe ischemia or infarction can lead to papillary muscle dysfunction or rupture and varying severity of mitral regurgitation. The posteromedial papillary muscle, in association with inferior infarction, is most commonly affected because it has a single blood supply. The anteromedial papillary muscle is less affected because of a dual blood supply. The peak occurrence of rupture is on days 2 to 4 after acute MI, and the clinical severity depends on the extent of damage to the papillary muscle apparatus and chordal structures. The most common clinical presentation is the appearance of a new systolic murmur and acute pulmonary edema. The presence of papillary muscle rupture and dysfunction is confirmed by echocardiographic demonstration of abnormalities in the mitral valve apparatus and severe mitral regurgitation. Vasodilatation and IABP insertion may assist with initial stabilization, and, even though the overall operative mortality is ~25%, immediate surgery is usually the best therapeutic option.

Ventricular Septal Defect and Cardiac Rupture

Both ventricular septal defect and free wall rupture are more likely in the elderly and in patients with systemic hypertension. Ventricular septal defects may occur with either anterior or inferior infarction and are more likely seen with extensive infarction. It usually occurs on days 3 to 7 following MI. The size of the defect and extent of left-to-right shunting determine the clinical

features. Patients with septal rupture are usually recognized by the development of shock and a new systolic murmur. Again, bedside echocardiography can document the location, size, and amount of shunt flow. Early surgery provides the best chance for survival.

Acute cardiac rupture can occur without warning and presents as sudden severe hypotension with a relatively unchanged ECG. It usually occurs 5 to 14 days after MI. Free wall rupture is usually a catastrophic event, and only emergent surgery will prevent death. Occasionally, rupture will be subacute with symptoms of pericardial pain, nausea, and persistent vomiting or acute agitation.

MURAL THROMBUS AND SYSTEMIC EMBOLI

The likelihood of mural thrombus formation and early systemic emboli are related to the size and location of the infarct. The *overall* frequency of mural thrombi is 20%, with a 2% risk of systemic emboli, but the risk is even higher if the LV apex is involved. For example, patients with a large anterior MI have a 60% prevalence of thrombus and a 6% risk of emboli. Because the embolic risk is substantially reduced with anticoagulation, patients with an anterior and apical infarction should receive heparin during their hospitalization and warfarin for at least 3 months after discharge. Reperfusion therapy resulting in a patent artery also reduces the occurrence of mural thrombosis.

ACUTE PERICARDITIS

Acute MI is the most common cause of acute pericarditis and is clinically recognized in ~10% to 20% of patients with an acute MI. It usually occurs on days 1 to 4 after MI. The clinical presentations range from detection of an asymptomatic friction rub to severe discomfort, fever, and associated atrial and ventricular dysrhythmias. Pericardial pain typically is different from the pain caused by infarction—it is sharper in quality, pleuritic, and varying in intensity with motion, swallowing, or coughing. Classically, the pain is relieved when sitting and may radiate to the left shoulder. On physical examination, there is a three-component pericardial friction rub, and the ECG demonstrates PR-segment depression and concave ST-segment elevation in multiple leads (see Figure 54.2 in Chapter 54). Aspirin (650 mg every 4 to 6 hours) can be effective in relieving symptoms. Other nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticosteroids should be avoided, as they can interfere with healing of infarcted myocardium.

Patients can also get a late pericarditis, also known as Dressler syndrome, 1 to 8 weeks following MI. This is secondary to immune-mediated injury and is also treated with aspirin. NSAIDs and corticosteroids can be used if it has been > 4 weeks since the patient's MI.

Pericarditis can also occur from other causes, such as pericardial irritation after thoracic or cardiac surgery. This should be recognized and distinguished from post-MI pericarditis. It is typically treated symptomatically with NSAIDs.

STRESS-INDUCED CARDIOMYOPATHY (TAKOTSUBO CARDIOMYOPATHY)

Stress-induced cardiomyopathy, also known as Takotsubo cardiomyopathy, is an important clinical syndrome that can mimic acute coronary syndromes. It is thought to be caused by a sudden catecholamine surge in the setting of extreme emotional stress. Patients can have chest pain, positive cardiac biomarkers, and ECG changes suggestive of an anterior wall myocardial infarction. Echocardiography shows a classic ballooning of the apex of the heart with preserved function of the base. This syndrome can cause congestive heart failure and ventricular arrhythmias.

As the syndrome mimics an acute myocardial infarction, it must be treated as such until a diagnosis can be made. These patients are often referred for urgent cardiac catheterization, which

reveals normal coronary arteries. The treatment that follows is supportive, as the syndrome, depressed ejection fraction, and wall motion abnormalities usually resolve.

CONSIDERATIONS FOR THE PATIENT UNDERGOING NONCARDIAC SURGERY

Not infrequently patients in the ICU develop a need for noncardiac operative intervention. Cardiac risk stratification is important because the risk for perioperative cardiac morbidity or mortality among patients who have had recent or active ischemia is high. Risk stratification should be accomplished in patients with suspected ischemia using a combination of clinical signs and symptoms as well as non-invasive methods such as stress testing (see more details in Chapter 86). These assessments may indicate a need for coronary angiography or revascularization with PCI or coronary artery bypass grafting prior to noncardiac surgery. Alternatively, if ICU patients require urgent operative intervention, prophylaxis against cardiac events should include judicious use of IV beta-blockers and nitrates perioperatively, as well as consideration for more invasive hemodynamic monitoring. Serial ECGs and myocardial enzymes should be obtained postoperatively, and antiplatelet therapies should be resumed as soon as bleeding risk is believed to be low enough from a surgical standpoint.

An annotated bibliography can be found at www.expertconsult.com.

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These two documents outline in detail the guideline-recommended evaluation and therapy for patients with unstable angina and non-ST-elevation myocardial infarction (NSTEMI). These recommendations were based on the latest evidence from clinical trial data.

CHAPTER 51

Thoracic Aortic Aneurysms and Dissections

Fenton McCarthy ■ Benjamin A. Kohl ■ Bonnie L. Milas

Aortic Aneurysms

The term *aneurysmal* is used when the luminal diameter of the aorta grows to 150% of the mean diameter, as measured in a normal population. The aortic wall, as with any artery, is composed of three distinct layers, which, extending from the lumen to the external wall, are termed the intima, media, and adventitia. *True aneurysms* involve all three layers of the aortic wall, whereas *pseudoaneurysms* involve only one or two. The latter typically result from a rupture contained by surrounding structures—for example, pleura, thrombus, or abscess wall. Aneurysms are called *fusiform* when the entire circumference of the aortic wall is dilated, whereas *saccular aneurysms* are localized and result from a small area of weakness within the aortic wall.

In the thorax, ~60% of aneurysms involve the ascending aorta (with or without arch or descending aortic involvement), ~30% are localized to the descending aorta, and only ~10%, mostly saccular, are found exclusively within the aortic arch. Thoracoabdominal aneurysms involve variable portions of both the thoracic (supradiaphragmatic) and abdominal (subdiaphragmatic) aorta.

Aortic Dissections

Aortic dissection is a condition in which blood extravasates from the aortic lumen, through a tear in the intima, and propagates within the aortic media. The adventitia becomes the only layer preventing a complete ("free") rupture. The newly created false lumen can dissect distally or proximally (retrograde) through the media until it reaches an area where the tissue is strong enough to counteract the propagating force within the dissection. At this point it either reenters the lumen through a new intimal tear (reentry point), decompressing the false channel, or the false channel becomes thrombosed because of sluggish flow. Intimal tears are usually easily identified by imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), or echocardiography.

COMPLICATIONS

The complications resulting from an aortic dissection can be catastrophic. Rupture into the mediastinum can occur anywhere along the dissected portion of the aorta. If the proximal ascending aorta ruptures, hemopericardium and potentially acute cardiac tamponade may result. Other serious complications can result from the expanding false lumen causing stenosis, occlusion, or continued propagation down branch vessels, compromising blood flow to the heart, brain, mesentery, liver, kidneys, spinal cord, or extremities. Finally, when the dissection involves the ascending aorta, the

Additional online-only material indicated by icon.

Aneurysms of the arch and descending thoracic aorta are frequently associated with atherosclerosis. In contrast, ascending aortic aneurysms are typically associated with bicuspid aortic valves, collagen-vascular defects, such as Marfan or Ehlers-Danlos syndrome, or less well-defined pathology, such as annuloaortic ectasia. Poststenotic aortic dilatation is an additional cause of ascending aneurysms thought to result from areas of the aortic wall exposed to flow derangements, usually as a result of aortic stenosis.

Microscopic findings in ascending aortic aneurysms commonly demonstrate fragmentation of elastin fibers within the media. As a result, the tensile strength of the aortic wall is reduced, leading to progressive dilatation. A dilated, thin ascending aorta is more prone to a disruption within the intima, which, in turn, can become the starting lesion for an aortic dissection. Other rare causes of thoracic aortic pathology include a variety of vasculitides (which more commonly cause occlusive disease), infections, trauma, and tertiary syphilis (which causes medial degeneration of the ascending aorta and aortic arch).

commissures of the aortic valve can be disrupted by the expanding false lumen, causing prolapse of the involved valve leaflet resulting in aortic insufficiency.

CLASSIFICATION

Aortic dissections were first classified by DeBakey according to the site of intimal tear and the extent of the false lumen within the aorta. A simpler and more clinically relevant classification was developed at Stanford and categorized dissections based on the region of the aorta involved (Table 51.1). Type A dissections include any dissections involving the ascending aorta. Such lesions may be isolated to the ascending aorta or may extend into the aortic arch and descending aorta. Type B dissections involve only the descending aorta (defined as aorta distal to the left subclavian artery). Type A dissections are frequently associated with chronic hypertension or some degree of annuloaortic ectasia or collagen-vascular defect, such as Marfan syndrome. Importantly, most type A dissections are not related to atherosclerotic disease. In contrast, patients with type B dissections typically have advanced atherosclerotic disease and labile hypertension. These patients are frequently older and often have serious comorbid conditions related to their profound systemic atherosclerosis.

TREATMENT

The Stanford group demonstrated better hospital survival in patients with type A dissections treated surgically, whereas medical therapy resulted in better survival rates for patients with type B dissections. As a result, emergent surgical repair is the therapy of choice for patients with type A dissections, whereas medical management is the preferred approach for patients with type B dissections, with surgery having only a limited role.

The goals of surgery in type A aortic dissections are related directly to the most frequent life-threatening complications associated with this disease. Specifically, by operating early, the intent is to avoid rupture of the ascending aorta (into the thorax or pericardium), prevent or correct malperfusion of the coronary arteries or the brachiocephalic vessels, and treat aortic insufficiency by repairing or replacing the aortic valve. Because it is not feasible to replace the entire segment of dissected aorta (frequently from the aortic valve proximally to the bifurcation of the iliac arteries distally), management of the residual dissected aorta is dictated by symptoms. For example, malperfusion syndromes are generally treated by extra-anatomic bypass.

Developments in thoracic endovascular repairs (TEVAR) have made stenting the descending aorta, particularly in regions of malperfusion, a viable option at some centers. To be a candidate for an endovascular procedure, the patient's iliac vessels must be able to accommodate device entry, and there must be relatively normal aortic diameter on either side of the lesion for the stent to adhere to (the so-called landing zone). Complications that are specific to endovascular procedures involve angiographic evidence of persistent flow within the aneurysmal sac after stent placement. The location and severity of this ongoing leak dictate subsequent therapy (see Box 51.E1).

TABLE 51.1 ■ **Stanford Classification of Thoracic Aortic Dissections**

Type	Description
Type A	Dissections involving the ascending aorta (may also involve the descending aorta)
Type B	Dissections involving *only* the descending thoracic aorta (distal to left subclavian artery)

BOX 51.E1 ■ Classification of Endoleaks after Thoracic Endovascular Aortic Repair (TEVAR)

TYPE I. Blood entering the aneurysmal sac at the apposition point of the proximal or distal most portion of the stent. Usually requires urgent intervention.

TYPE II. Blood entering the aneurysmal sac via retrograde flow from collateral vessels (usually intercostal arteries). Usually resolves without intervention.

TYPE III. Blood entering the aneurysmal sac in areas where stents have torn or inadequately overlap. Usually requires further balloon dilatation or additional stent placement.

TYPE IV. Blood entering the aneurysmal sac through the porous graft material. Very rare with current generation stents.

TYPE V. Continued aneurysmal sac dilation (presumably resulting from continued blood leakage) without evidence of an endoleak. Additional workup is necessary to identify etiology.

Data from Gleason TG: Endoleaks after endovascular aortic stent-grafting: impact, diagnosis, and management. Sem Thor Cardiovasc Surg 21:363–372, 2009.

BOX 51.1 ■ Diagnostic Considerations for Aortic Aneurysms

Asymptomatic (in most cases)
Aortic valvular insufficiency
Chest pain (anginal pain may occur if coronary blood flow is compromised)
Dysphagia
Dyspnea (resulting from compression of the trachea)
Hemoptysis
Hoarseness (caused by pressure on left recurrent laryngeal nerve)
Wheezing (caused by tracheal compression)

Surgical treatment in type B dissections is primarily indicated when there is ongoing malperfusion not amenable to TEVAR or, when present, to treat acute aortic rupture.

Traumatic Aortic Injuries

When penetrating injuries involve the ascending aorta, they are usually fatal. Blunt injuries to the aorta can also cause disruption of the ascending aorta, which, when severe enough, are also usually lethal. Deceleration injuries to the *descending* aorta usually occur just distal to the origin of the left subclavian artery at the aortic isthmus. Injuries in this region are frequent because at this point, the aorta is fixed to the posterior chest wall by the intercostal arteries and anteriorly to the pulmonary artery by the ligamentum arteriosum (the embryologic remnant of the ductus arteriosus). Sudden deceleration of the thorax applies stress to the aorta at these points of fixation. If the aorta completely ruptures, immediate exsanguination and death usually result. However, if the rupture is partially contained (often by parietal pleura), the patient may survive long enough to get to a hospital (a contained aortic disruption). Ultimately, the patient's survival depends on prompt diagnosis and treatment (see Chapters 98 and 101).

Diagnostic and Clinical Considerations

Most aortic aneurysms are asymptomatic until late in their course. As a consequence, they are usually detected as incidental findings during medical evaluation. When symptoms develop, they usually relate to rapid growth or pressure on surrounding structures (Box 51.1).

The hallmark presentation of *acute aortic dissection* is sharp (or "tearing"), severe pain that is either retrosternal or midscapular in location (Box 51.2). The pain typically radiates down the patient's back as the dissection propagates and may also be accompanied by syncope, diaphoresis, or hypotension.

Traumatic aortic disruption may be difficult to detect. Severely injured patients often have multisystem trauma and, because of their many distracting injuries, are unable to report retrosternal or intrascapular pain. Therefore, a high index of suspicion must be maintained based on the physical evidence of trauma and the mechanism of injury. Signs associated with a contained aortic disruption are listed in Box 51.3.

DIAGNOSIS

The diagnosis of an aortic pathologic condition is usually confirmed by chest computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance angiography scan (MRA), or transesophageal echocardiography (TEE).

The diagnostic modality one chooses to employ typically depends on local availability, institutional practice patterns, and clinical context. Although aortography was used extensively in the past, it is now usually reserved for elective delineation of abdominal visceral blood supply or to image stable traumatic aortic disruptions. Preoperatively, the coronary anatomy should be defined by cardiac catheterization, particularly in older patients who have a history of angina or a positive stress test, or if acute electrocardiographic (ECG) or clinical findings suggest acute myocardial ischemia. Similarly, if clinical circumstances permit, preoperative carotid or peripheral vascular studies are warranted in patients with atherosclerotic aortic disease.

BOX 51.2 ■ Diagnostic Considerations for Acute Aortic Dissections

Type A or B Dissections

- Diaphoresis
- Hypotension
- Radiation of pain to back or abdomen
- Severe retrosternal or midscapular pain
- Syncope

Type A Dissections

- Aortic insufficiency murmur
- Ischemic electrocardiographic changes
- Signs of cardiac tamponade
  - —Distant heart sounds
  - —Electrical alternans
  - —Elevated jugular or central venous pressure
  - —Hypotension
  - —Pulsus paradoxus
- Hemiplegia or visual changes
- Absent upper extremity pulses or blood pressure differential

Type B Dissections*

- Abdominal pain, metabolic acidosis, or melena (caused by mesenteric ischemia)
- Absent lower extremity pulses
- Motor or sensory deficit isolated to one limb
- Oliguria, anuria, rising BUN and creatinine levels (caused by renal ischemia)
- Paraplegia (caused by anterior spinal cord ischemia)

**Also applies to type A dissections extending past the left subclavian artery.*
BUN, blood urea nitrogen.

BOX 51.3 ■ When to Suspect Traumatic Aortic Rupture

- Postdeceleration injury
- Evidence of anterior chest wall injury
- Hypotension
- Increased output of blood flow via chest tube
- Pulse deficit or blood pressure differential in limbs
- Widened mediastinum on chest radiograph

MEDICAL MANAGEMENT (Box 51.4)

The greatest risk for patients with acute thoracic aortic pathology is abrupt hemodynamic decompensation or exsanguination because of leakage or rupture of the aorta. Box 51.4 lists the immediate preoperative management priorities.

There are two critical pharmacologic objectives: (1) meticulous control of blood pressure aiming for a systolic blood pressure of 105 to 115 mm Hg and (2) simultaneous reduction of myocardial ejection velocity so that aortic shear forces are decreased. For the former, blood pressure control should be achieved by continuous intravenous (IV) infusion of rapidly acting vasodilators, such as nitroprusside or nicardipine. To reduce myocardial ejection velocity, one should give a rapidly acting, easily titratable beta-blocker—for example, a continuous IV infusion of esmolol.

Labetalol is a particularly efficacious drug, as it achieves both objectives because of its combined alpha- and beta-adrenergic receptor blockade. If beta-blocker therapy is strongly contraindicated, one can use verapamil to achieve the same goals.

The risk of using vasodilators alone is that myocardial ejection velocity will increase because of the acute reduction in afterload and thus decreased resistance to left ventricular ejection. Concurrent beta-blockade *must* be instituted with vasodilator therapy to decrease the risks of dissection propagation or aneurysm rupture. Finally, control of pain with opioids is an important adjunct to vasodilator therapy and beta-blockade.

Determination of end-organ perfusion and function, including mental status, urine output, and the presence of abdominal or extremity pain, should be assessed frequently until definitive repair is performed or symptoms are controlled (Box 51.5).

BOX 51.4 ■ Medical and Preoperative Management of Thoracic Aortic Disease

- Insert two large bore IV catheters
- Type and cross for six units of red blood cells
- Insert arterial catheter in limb with highest blood pressure
- Monitor end-organ perfusion (see Box 51.5)
- Monitor limb pulses
- Vasodilator therapy by continuous IV infusion to keep systolic blood pressure within the 105 to 115 mm Hg range (e.g., sodium nitroprusside or nicardipine)*
- Concomitant beta-blocker therapy to keep heart rate at 60–80/min and cardiac index at 2–2.5 L/min/m^2 (e.g., IV infusion of esmolol)*
- Preoperative pain management using opioids, but avoid obtundation to allow serial neurologic examinations
- Volume resuscitation
- Chest radiograph

**See the text and Chapter 53 for details of their usage.*
IV, intravenous.

BOX 51.5 ■ Monitoring End-Organ Perfusion

Cardiac

- 12-lead ECG
- Presence and degree of anginal pain
- Signs of aortic insufficiency and congestive heart failure
- Signs of cardiac tamponade

Neurologic

- Level of consciousness
- Motor or sensory deficit

Gastrointestinal

- Abdominal examination
- Liver function studies
- Coagulation profile

Renal

- BUN and creatinine levels
- Hourly urinary output

ECG, electrocardiogram; BUN, blood urea nitrogen.

POSTOPERATIVE CARE (Box 51.6)

Control of Blood Pressure and Blood Loss

As a first priority, one must continue to control blood pressure meticulously to avoid disruption of newly created aortic suture lines and to decrease the risk of rupture of the residual dissected aorta. The patient with excessive bleeding postoperatively should first be warmed and have any coagulation deficits corrected. If the chest tube output of blood exceeds 400 mL/hour in 1 hour, > 300 mL/hour for 2 to 3 hours, or > 200 mL/hour for 4 hours, surgical reexploration should be considered.

End-Organ Evaluation

After surgical repair, end-organ performance must be monitored closely to ensure adequacy of perfusion to the entire vascular tree. The same clinical and laboratory indicators that were used in the preoperative period should be used postoperatively to determine the adequacy of end-organ perfusion (see Box 51.5).

Spinal cord ischemia is of particular concern in patients who have surgery on the descending thoracic aorta or proximal abdominal aorta. Perfusion of the spinal cord via collateral vessels can be augmented by maintaining a *mean* arterial pressure of > 80 mm Hg or by reducing the surrounding intrathecal pressure by draining cerebrospinal fluid using a lumbar drain.

A neurologic examination should be performed as soon as the patient is responsive in the ICU because both the brain and spinal cord are at risk from interruption of blood flow or embolization of atherosclerotic debris or air. If a cerebrospinal drainage catheter was placed for surgery and an elevated cerebrospinal fluid pressure is noted postoperatively, cerebrospinal fluid drainage may be indicated. After the patient has remained hemodynamically and neurologically stable for 12 to 24 hours, the lumbar drain should remain in place but not drained for an additional 12 to 24 hours. If, after this period, the patient has not exhibited signs of spinal cord ischemia, the drain can be carefully removed and the patient should remain supine for 4 to 6 hours after removal. If, however, weakness develops during the period when the drain remains in place, attempts should

BOX 51.6 ■ Postoperative Management of Thoracic Aortic Surgical Patients

Perform same interventions as preoperative care (Table 50.5) except as noted below.
For patients with potential intraoperative spinal cord ischemia (distal descending thoracic aortic repairs), maintain mean blood pressure > 80 mm Hg.
Assess for bleeding and coagulopathy.
Monitor end-organ perfusion (same as Table 50.6) except as noted below.
Complete neurologic examination when patient is responsive.
If patient is unresponsive, check for residual neuromuscular blocker effect by twitch monitor.
If residual neuromuscular blocker effect is present, reverse neuromuscular blocker.
If still unresponsive, pharmacologically reverse benzodiazepines and opioids.
If still unresponsive, obtain neurologic consultation and STAT head CT scan without contrast or brain MRI with contrast.
If patient has focal neurologic deficit, obtain neurologic consultation and STAT head CT scan without contrast or brain MRI with contrast.
If patient has signs of spinal cord injury, obtain MRI of spinal cord and somatosensory-evoked potential tests.
Epidural anesthesia is preferred for postthoracotomy patients for pain management.
Perform postoperative spinal drainage to decrease ICP if elevated.

CT, computed tomography; MRI, magnetic resonance imaging; ICP, intracranial pressure; STAT, immediately.

be made to drain cerebrospinal fluid (CSF) to maintain an intracranial pressure (ICP) < 10 cm H_2O and increase mean arterial pressure to > 100 mm Hg (if possible), and immediate consultation with the neurology service is warranted.

A patient who remains unresponsive 6 to 12 hours following aortic surgery requires further evaluation. After confirming that no residual neuromuscular blockade is present and that the neurologic depression is not due to narcotics or benzodiazapines, a formal neurologic consultation and noncontrast head CT scan (to avoid contrast-induced renal injury) or MRI scan of the brain should be immediately obtained. Although a bland infarction would not usually be detectable by CT scan until postoperative day 2 or 3, an intracranial hemorrhage could be visualized immediately postoperatively. An MRI of the spinal cord should be considered after descending aortic surgery to assess for spinal cord injury.

Pain Management

Neuraxial analgesia can be an effective modality but should be instituted only after hemodynamic stability is attained, bleeding has subsided, and the absence of neurologic injury has been confirmed. Great care must be taken with epidural analgesia, as the resultant pharmacologic sympathectomy can cause profound hypotension and may lead to spinal cord ischemia.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 52

Acute Heart Failure Syndromes

Lee R. Goldberg ■ Esther Vorovich

Since the 1980s, the incidence and prevalence of chronic heart failure have been increasing rapidly with estimates showing ~1% to 2% of the U.S. population being affected, predominantly in patients older than 65 years. This increase can be attributed to a combination of an aging population with increasing incidences of risk factors for heart failure (e.g., hypertension and diabetes), improved survival postmyocardial infarction (Chapter 50), and improved prevention of sudden cardiac death. The result is a higher prevalence of patients living with, rather than dying from, myocardial dysfunction.

With this rise in the number of patients with ventricular dysfunction, there has been a concomitant and expected rise in hospitalizations for acute heart failure syndromes (AHFS). More than 1 million hospitalizations occur in the United States annually for the primary diagnosis of heart failure, representing an ~threefold increase over previous decades. This chapter focuses on the pathophysiology, diagnosis, and management of acute heart failure syndromes.

Definition and Classification

Acute heart failure syndromes are a heterogeneous group of disorders that share a similar clinical presentation. The latter is broadly defined as signs and symptoms of progressive heart failure that require inpatient hospitalization for urgent or emergent treatment. The majority of these hospitalizations occur in patients with known chronic heart failure (80%). Whereas previously AHFS was thought to predominantly affect patients with systolic dysfunction, large registry data from the United States and Europe have shown that approximately half of the patients admitted with AHFS in fact have heart failure with preserved ejection fraction (HFpEF).

The clinical presentation of heart failure is varied with ~75% of patients presenting with normal or elevated blood pressures and only a small minority presenting with cardiogenic shock or cardiogenic pulmonary edema. Numerous classification schemes have been created in an attempt to categorize this diverse group of patients by etiology, presentation, chronicity, or presumed reversibility. However, this chapter uses the classification system proposed by the American College of Cardiology/American Heart Association (ACC/AHA) that focuses on these two metrics used in the clinical assessment of myocardial function: (1) volume status and (2) tissue perfusion.

Prognosis

Prognosis of AHFS can be divided into three distinct categories: in-hospital (inpatient) mortality, postdischarge morbidity and mortality, and longer-term morbidity and mortality. Inpatient mortality rates for patients with AHFS, excluding the cardiogenic shock subset (discussed in Chapter 8), typically range from 3% to 7%. Large registry data sets from the United States have identified several key factors as predictors of in-hospital mortality. The Acute Decompensated Heart Failure National Registry (ADHERE identified three variables present on admission as associated

Additional online-only material indicated by icon.

with in-hospital mortality: blood urea nitrogen (BUN) > 43 mg/dL, lower systolic blood pressure (< 115 mm Hg), and elevated serum creatinine (> 2.75 mg/dL). A separate registry, the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, also identified serum creatinine and lower systolic blood pressure (SBP) as predictors of in-hospital mortality with the addition of several other variables (age, heart rate, presence of LV dysfunction and serum sodium). Subsequent analyses have also shown several other variables to be associated with in-hospital mortality including elevated brain natriuretic peptide (BNP), elevated troponin, and the need for inotropic therapy. Despite adequate symptom relief during the inpatient hospitalization, postdischarge readmission and mortality rates remain high (10% to 20% and 20% to 30%, respectively). Multiple variables associated with short-term readmissions and mortality have been identified, including systolic blood pressure, admission creatinine and hemoglobin, tachycardia, prolonged QRS, new onset arrhythmia during admission, worsening renal function during or after hospitalization, discharge hyponatremia, and discharge use of evidence-based therapies (angiotensin-converting enzyme [ACE]-I inhibitors, angiotensin receptor blockers [ARBs], beta-blockers) among others. Regarding long-term mortality, the data are not as robust but show that each hospitalization for acute heart failure (AHF) negatively impacts prognosis in an additive fashion (Figure 52.E1). Not surprisingly, variables identified as having an impact on long-term prognosis in chronic heart failure, such as elevated BNP, QRS duration, and kidney dysfunction, have been shown to affect long-term prognosis after an episode of AHF.

Pathophysiology

CARDIAC OUTPUT AND MEAN ARTERIAL PRESSURE

Cardiac output (cardiac index is normalized for body surface area [BSA]) expressed in liters of blood per minute is determined by the product of stroke volume and heart rate (see Equation 1 in this chapter and Table 8.1 in Chapter 8). The heart rate is determined by the patient's underlying electrical rhythm and balance of sympathetic and parasympathetic inputs, which in turn are often driven by the patient's clinical status. The stroke volume is determined by the three principal factors: preload, intrinsic myocardial contractility, and afterload (see Figures 8.2 and 8.3 in Chapter 8).

Mean arterial blood pressure (MAP), the main driving force governing tissue perfusion, is defined by the following relationship between systemic vascular resistance (SVR) and cardiac output (CO):

$$\text{MAP} = (\text{CO} \times \text{SVR}) + \text{Central venous pressure (CVP)} \qquad \text{(Equation 1)}$$

Mean arterial pressure can be easily calculated from bedside blood pressure (BP) measurements using the following formulas (that are equivalent mathematically):

$$\text{MAP} = 1/3\ \text{Systolic BP} + 2/3\ \text{Diastolic BP} \qquad \text{(Equation 2A)}$$

or

$$\text{MAP} = \text{Diastolic BP} + 1/3\ (\text{Systolic BP} - \text{Diastolic BP}) \qquad \text{(Equation 2B)}$$

In patients with AHF, although the MAP guides treatment options, systemic vascular resistance (SVR) is the true target of pharmacologic afterload reducing therapies. SVR is a calculated value obtained from invasive hemodynamic monitoring and is a cornerstone in the hemodynamic-guided therapy of patients with refractory decompensated heart failure. As should be evident from these equations, MAP and SVR are not synonymous terms but rather reflect the interplay between cardiac output and vascular tone. SVR (commonly expressed in dyn · s cm^{-5}) is calculated by the following formula:

$$\text{SVR} = [(\text{MAP-CVP})/\text{CO}] \times 80 \qquad \text{(Equation 3)}$$

In *systolic* heart failure, an inciting event (e.g., myocardial infarction, myocarditis, hypertensive crisis) results in myocardial dysfunction. This dysfunction results in activation of numerous

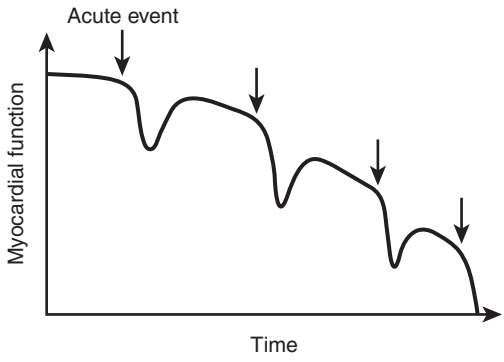


Figure 52.E1 The effect of AHF exacerbations on myocardial function over time. *(From Gheorghiade M, De Luca L, Fonarow GC: Pathophysiologic targets in the early phase of acute heart failure syndromes. Am J Cardiol 96(Suppl):11-17, 2005.)*

In Figure 8.2, the classic "Frank-Starling curves" demonstrate that with increasing left ventricular filling pressure (LVEDP), or preload, there is a concomitant increase in cardiac output via the mechanism of increasing stroke volume. This relationship is maintained at low, normal, and mildly elevated filling pressures with subsequent flattening of the slope of the curves at higher filling pressures indicating a "limit" to the ability of the heart to augment stroke volume at the extremes of filling pressures. Whereas line A represents normal myocardial contractility, line C represents depressed myocardial functioning with subsequent lower cardiac outputs at any given filling pressure as well as a flatter slope indicating a decreased ability to augment stroke volume in the setting of myocardial dysfunction. It is important to note that although the slope of the line flattens, there is no descending limb to the curves indicating decreasing stroke volumes at excessively high filling pressures. However, these studies were performed in isolated myocytes rather than in whole hearts. Although myocytes continue to increase their contractility with increasing "stretch" or filling pressures, elevated filling pressures exert a negative impact on global left ventricular (LV) functioning. At high filling pressures, there is neurohormonal activation, distortion of LV architecture, stretching of the papillary muscles, and subsequent induction of functional mitral regurgitation that leads to the phenomenon colloquially termed "falling off the starling curve." Figure 8.3 illustrates a similar but opposite relationship between afterload and SV showing that with increasing afterload, SV decreases. Importantly, curve C, which again represents depressed myocardial contractility, shows a significantly steeper slope indicating a more pronounced negative effect of afterload on SV and CO in the setting of myocardial dysfunction.

compensatory mechanisms in an attempt to maintain cardiac output and tissue perfusion. One of the first mechanisms invoked is an increase in sympathetic activation with a concomitant decrease in parasympathetic activity. This results in higher norepinephrine levels that, in the short term, increase CO via increasing contractility and heart rate and maintain blood pressure via both increasing CO as well as inducing peripheral vasoconstriction. The increased sympathetic activation in addition to other stimuli also stimulates activation of the renin-angiotensin system (RAS). Stimulation of the RAS induces sodium reabsorption in the kidney, peripheral vasoconstriction, and aldosterone secretion as well as positive feedback to further increase sympathetic activation, all of which function to maintain CO in the short term. This leads to salt and water retention and increased preload. Counter regulatory mechanisms, such as secretion of brain and atrial natriuretic peptides (BNP and ANP), are invoked in an attempt to counteract the effects of RAS activation. However, these mechanisms appear to be less effective in patients with heart failure.

In the long term, the increased sympathetic and RAS activation lead to multiple deleterious effects on the heart such as myocyte hypertrophy, fibrosis, and necrosis as well as increased arrhythmic risk resulting in further decrements in cardiac function and performance. In response to the initial insult coupled with the subsequent neurohormonal activation, the LV undergoes negative remodeling with changes in myocyte biology, myocardial structure, and LV chamber geometry. Macroscopically, the LV becomes dilated and spherical (rather than elliptical), causing "stretching" of the papillary muscles inducing functional mitral regurgitation as well as increasing wall stress. This in turn leads to increased oxygen utilization while also decreasing cardiac output, which results in further activation of the neurohormonal compensatory systems.

In HFpEF, although the contractile function of the heart may be grossly normal, a low cardiac output results from a ventricle that has a thick wall but small cavity size. The left ventricle tends to be stiff and relaxes slowly throughout diastole leading to elevated end diastolic pressures. This pressure is reflected backward into the pulmonary veins and then pulmonary capillaries leading to dyspnea on exertion and ultimately elevated right-sided pressures and the development of edema. The elevated pressures and decreased cardiac output activate similar neurohormonal pathways seen in systolic heart failure including activation of the sympathetic and RAS.

PATHOPHYSIOLOGY OF ACUTE HEART FAILURE

Multiple precipitating factors have been identified for AHFS (Box 52.E1). All of these factors lead to either increased volume and congestion or decreased myocardial systolic or diastolic performance. Once the inciting event occurs, neurohormonal activation is increased, leading to increased myocardial oxygen demand (and possible ischemia resulting from supply/demand mismatch [Chapter 50], peripheral vasoconstriction, and sodium and water retention in a positive feedback loop. If left uncorrected, these changes lead to further decrements in myocardial function, organ hypoperfusion, and eventual cardiogenic shock (Chapter 8). Although this cycle pertains to all patients with AHFS, patients with obstructive coronary artery disease are particularly susceptible to the development of ischemia secondary to supply-demand mismatch in the setting of increased myocardial oxygen demand with concomitant drops in coronary perfusion pressures (as a result of either hypotension or elevated LV diastolic pressures).

Clinical Presentation and Initial Assessment

Evaluation of any patient with known or suspected cardiac dysfunction involves a careful history and physical examination focusing on three vital components: (1) assessing volume status, (2) assessing tissue perfusion, and (3) evaluating for precipitating factors and comorbidities.

BOX 52.E1 ■ Factors That Can Precipitate Acute Heart Failure

Nonadherence with medial regimen or diet
Myocardial ischemia/infarction
Uncontrolled blood pressure
Arrhythmias (atrial fibrillation, ventricular arrhythmias, bradycardias)
Introduction of negative inotropic agents (beta-blockers, nondihydropyridine), glitazones, or NSAIDs
Substance abuse (alcohol or illicit drug use)
Endocrine abnormalities (diabetes, thyroid disease)
Infection/sepsis
Progressive cardiac dysfunction
Progressive valvular dysfunction
Right ventricular pacing
Noncardiac organ dysfunction (renal, pulmonary)
Anemia
Pulmonary embolus
Obstructive sleep apnea
Aortic dissection
Pericardial tamponade
Surgery

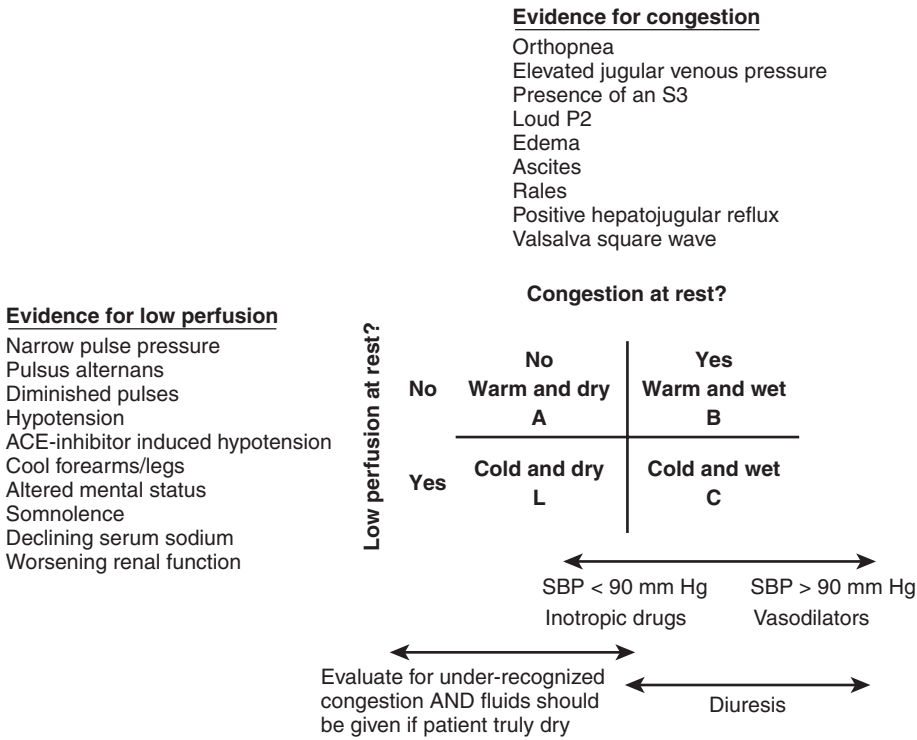


Figure 52.1 Hemodynamic assessment of patients with AHF. Profile A patients show no signs of hypoperfusion or congestion and should be evaluated for other etiologies of their symptoms. Profile B patients have evidence of congestion but maintain their perfusion. This group of patients should be diuresed and continued on their home medications unless blood pressure permits up-titration of home vasodilators. Profile C patients show evidence of congestion and hypoperfusion. These patients should be "warmed up" using vasodilators or inotropic therapy (depending on blood pressure) and then diuresed. Profile L patients show evidence of hypoperfusion without evidence of congestion. Profile L constitutes a small minority of patients presenting with AHF and they should be evaluated for under-recognized congestion and given IVF if truly "dry." Inotropic therapy may be considered but remains a poor long-term option.

A typical approach to the initial assessment is depicted in Figure 52.1 in which patients are grouped into four hemodynamic profiles. The patients in profile A are euvolemic and well perfused and represent well-compensated outpatients, management of whom is outside the scope of this chapter. Based on registry data in the United States and Europe, the majority of patients admitted for AHF present with symptoms of congestion (Table 52.E1), in particular dyspnea as represented by profiles B and C. As patients with chronic heart failure develop multiple adaptive responses to chronically elevated filling pressures, congestion is often under-recognized on examination. The sensitivities of findings commonly associated with congestion such as rales, edema, or an abnormal chest chest radiograph have sensitivities of < 30% for detecting congestion in patients with chronic heart failure. In contrast, an elevated jugular venous pressure (JVP) or positive hepatojugular reflux, which in the absence of pulmonary hypertension or right-sided heart failure mirrors left-sided filling pressures, has a sensitivity of 80% for detecting a pulmonary capillary wedge pressure of > 18 mm Hg.

Profiles C and L in Figure 52.1 represent the patients with low perfusion with and without congestion, respectively. Low output heart failure and in particular cardiogenic shock patients constitute a minority of patients admitted with AHF. In contrast to patients with congestion who present with the typical symptoms listed in Table 52.E1, patients with hypoperfusion or

TABLE 52.E1 ■ **Signs and Symptoms of Congestion and Low Perfusion (also see Figure 52.1)**

Signs and Symptoms Predominantly Related to Congestion		***Signs and Symptoms Predominantly Related to Low Perfusion***	
Symptoms	**Signs**	**Symptoms**	**Signs**
Dyspnea	Elevated JVP	Fatigue	Narrow pulse pressure
Orthopnea	Positive hepatojugular reflux	Drowsiness	Hypotension
Paroxysmal nocturnal dyspnea (PND)	Lower extremity edema	Presyncope	Cool extremities
Cough	Rales	Syncope	Low volume ("thready") pulses
Wheezing	Pleural effusions	Confusion	Pallor
Lower extremity edema	Ascites		Dusky skin
Abdominal pain/ bloating	RUQ pain		Livedo reticularis
Early satiety	Hepatomegaly/splenomegaly		Pulsus alternans
	Icterus		
	Increased weight		
	S3 gallop		
	Loud P2		

JVP, jugular venous pressure; RUQ, right upper quadrant; S3, third heart sound; P2, pulmonary valve closure sound.

Adapted with modification from Braunwald E, Bonow R, Mann D, et al: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Philadelphia: Elsevier Saunders, 2008.

low output heart failure typically present with more nonspecific symptoms such as fatigue and lethargy. The constellation of vague symptoms, especially if combined with symptoms less classically thought to be due to heart failure such as abdominal pain and bloating, often lead to the misdiagnosis or delayed diagnosis of the low output state. Other historical or laboratory clues to low perfusion include new diuretic resistance as an outpatient, hyponatremia, elevated creatinine, or abnormal liver function tests as described later. In addition, blood pressure and heart rate can be important clues to hypoperfusion. Sinus tachycardia in the absence of an alternate cause (pain, pulmonary edema, hypovolemia, etc.) is an ominous finding often indicating significantly depressed cardiac function with an inability to augment stroke volume and subsequent reliance on heart rate to maintain cardiac output (see Figure 52.E1).

Hypotension in the setting of AHFS indicates hypoperfusion and likely cardiogenic shock. However, normotension can be seen in both low and normal perfusion states depending on the severity of cardiac dysfunction and concomitant increases in systemic vascular resistance. This further underscores the need for a careful and thorough physical examination with a particular focus on signs of hypoperfusion such as narrow pulse pressure, cool extremities, and diminished pulses on palpation. Correctly identifying patients with hypoperfusion is critical to the appropriate triaging and treatment of this select subgroup, which typically requires intravenous (IV) therapies and an intensive care unit (ICU) level of care. In addition, it is this group that benefits most from invasive hemodynamic monitoring.

As part of the initial assessment, one should always attempt to identify a possible precipitant cause. Box 52.E1 lists the common precipitants of AHFS, the most common of which is medication or dietary nonadherence. In addition, use of medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), certain calcium channel blockers, and other medications that can lead to volume retention are frequent causes of heart failure decompensation. Several of the precipitants, such as ischemia, arrhythmias, and pericardial tamponade (Chapter 54), need urgent or emergent treatment without which the AHFS will only progress in severity. Identifying a precipitating factor is not always possible but, if present, is imperative not only for directing in-hospital treatment but also for delivering appropriate patient counseling or medication adjustments on discharge.

LABORATORY AND NON-INVASIVE TESTING

All patients presenting with AHFS should have basic laboratory testing performed, including serum electrolytes, measures of renal function and liver injury, as well as a complete blood cell count. Evaluating renal function is critical in any patient presenting with AHFS. Renal insufficiency, which could be either a result of the AHFS or a precipitating cause, portends a worse prognosis and helps guide treatment decisions. Elevations in serum creatinine typically reflect a decrease in glomerular filtration rate (GFR), whereas elevations in BUN reflect not only a decrease in GFR but also the neurohormonal activation that results in downstream sodium and urea reabsorption in the proximal tubule. As result, it is common to see a relative increase in BUN versus creatinine levels in patients with AHFS, and not surprisingly, registry data have borne out BUN to be a significant predictor of in-hospital mortality.

In addition to creatinine and BUN, other relevant laboratory values include serum sodium and potassium. Hyponatremia, also often a reflection of neurohormonal activation, is present in 25% of patients admitted with AHFS and portends a worse prognosis. Multiple medications commonly prescribed for patients with chronic heart failure such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), aldosterone antagonists, and diuretics can affect potassium levels, and hypo- or hyperkalemia should be promptly corrected. Mild elevations in liver enzymes are often seen as a result of right-sided congestion. However, markedly elevated enzymes indicate either hypoperfusion or primary liver injury including drug

toxicity. A routine complete blood count should also be performed to rule out anemia and to aid in evaluating for the possibility of infection as a precipitating mechanism.

Troponin assays should be performed in any patients in whom ischemia or infarction is suspected. In patients with AHFS, troponin elevation is common and portends a worse prognosis. However, the troponin elevation is typically a result of myocardial damage caused by the acute heart failure (AHF) episode rather than a reflection of clinically relevant infarction that precipitated the decompensation. The natriuretic peptides are released by myocytes in response to stress (pressure or volume overload) in a dose-dependent manner and have been shown to have diagnostic and prognostic discrimination in AHFS. Unfortunately, multiple confounders interact with natriuretic levels, so it is critical to interpret their levels in the clinical context of the patient.

All patients with AHF should have an electrocardiogram (ECG) performed to evaluate for ischemia/infarction and arrhythmias, both of which are known to precipitate heart failure exacerbations. Although atrial fibrillation is commonly seen in ~20% to 30% of patients, the most common arrhythmia remains sinus tachycardia. The majority of patients admitted with AHFS present via the emergency department and with complaints of dyspnea. As such, most patients should have a chest radiograph performed. As mentioned previously, patients with chronic heart failure develop multiple adaptive processes to deal with chronically elevated filling pressures such as increased thoracic lymphatic capacity for fluid removal. As a result, a negative chest radiograph does not rule out elevated filling pressures or AHF but does aid in evaluating for noncardiac causes of dyspnea.

The cornerstone of cardiac imaging for AHF remains echocardiography, which can help to evaluate for precipitating causes (e.g., pericardial tamponade, new wall motion abnormality) to assess current cardiac systolic and diastolic function, valvular functioning and to provide noninvasive estimates of hemodynamic parameters (filling pressures, pulmonary vascular resistance [PVR]). Patients with known chronic heart failure, echocardiographic studies completed within the previous 6 months, and an identifiable precipitating factor do not need routine repeat echocardiograms. Other cardiac imaging including cardiac magnetic resonance imaging (MRI), nuclear imaging, and stress echocardiography should not be ordered routinely but can be performed in select cases to evaluate for ischemia, viability, myocardial infiltration or inflammation, or if any questions remain regarding myocardial function or anatomy.

CARDIAC CATHETERIZATION

Patients presenting with AHF in the setting of acute coronary syndrome (ACS) should urgently undergo coronary angiography if contraindications are not present. Although the routine use of pulmonary artery catheters (PACs) or Swan Ganz catheters is not recommended for the diagnosis or initial management of patients with heart failure, PACs can serve a crucial role in select complex cases (discussed later).

DE NOVO ACUTE HEART FAILURE (OR AN ABRUPT DECLINE IN STABLE CHRONIC HEART FAILURE)

In patients presenting with new-onset acute decompensated heart failure without a prior known history or in patients with known chronic heart failure with a new significant change in clinical status, the initial assessment and testing should be broadened. In patients with de novo heart failure and chest pain, obstructive coronary artery disease (CAD) should be ruled out with coronary angiography. In patients with new heart failure and no angina, coronary computed tomography (CT) angiography or stress testing can be considered depending on the pretest probability and clinical scenario. In addition to evaluating for CAD, patients should be evaluated for the presence of thyroid disease (hypothyroidism or hyperthyroidism), anemia, valvular heart disease,

arrhythmia, HIV, and, if clinical suspicion is present, hemochromatosis or autoimmune diseases. In patients with a history of well-compensated, nonischemic or ischemic cardiomyopathy who experience an abrupt decline in their health status, evaluation for new CAD, anemia, or thyroid dysfunction should be repeated.

Management

The goals of treating *chronic* heart failure are to decrease neurohormonal activation, prevent congestion, promote positive ventricular remodeling, and retard heart failure progression and death. In contrast, the goals of *acute* heart failure treatment are to (1) improve the hemodynamic status of the patient by decreasing filling pressures and improving cardiac output thereby stabilizing organ functioning and relieving symptoms, (2) identify and treat any potential contributors to the acute decompensation that could prevent future decompensation, (3) ensure evidence-based therapies are being prescribed, and (4) provide patient education.

Management of patients with AHFS can be divided into three stages: (1) early phase, (2) in-hospital phase, and (3) predischarge phase.

EARLY PHASE

The goals of the early phase of treatment include stabilization of vital signs, restoration of organ perfusion, and rapid relief of symptoms. The assessment in terms of the hemodynamic profiles described previously (see Figure 52.1) guides initial treatment choices. Profile B, the "warm and wet" patients, should be aggressively diuresed. Profile C, the "cold and wet" patients, need to be "warmed up" before diuresis with either vasodilators if their blood pressure is sufficient or with inotropes or vasopressor agents if their blood pressure is marginal or low. Regarding blood pressure characterization, it is important to note that there is no accepted cutoff value for normal blood pressure. Although an SBP of 90 mm Hg is typically considered hypotensive, patients with chronic heart failure, especially those on evidence-based therapies such as ACE inhibitors and beta-blockers, tend to have lower blood pressures, often below the 90 mm Hg cutoff. As such, treatment decisions in this group should be made on an individual case basis using the blood pressure value in conjunction with physical exam signs and symptoms evaluating for hypoperfusion. Profile L, the "cold and dry" patients, should be evaluated for the presence of hypovolemia or under-recognized hypervolemia. In addition, late or "cold" septic shock can present similarly and should be ruled out. If, in fact, the clinical presentation is deemed to have a cardiogenic etiology, this subgroup typically needs inotropes or vasopressors for stabilization.

NON-INVASIVE VENTILATION

Patients presenting with moderate to severe dyspnea are often initiated on morphine and oxygen therapy in the emergency department. If hypoxemia or respiratory distress persists, more aggressive forms of ventilation and oxygenation are indicated to alleviate symptoms and restore adequate gas exchange. Therapy with non-invasive ventilation (NIV), including continuous positive airway pressure (CPAP) or non-invasive intermittent positive pressure ventilation (Chapter 3), has been evaluated in numerous studies in patients presenting with acute cardiogenic pulmonary edema. Early trials showed improvement in symptoms and decreased rates of mechanical ventilation, but conflicting results in regard to mortality. Meta-analyses of these studies demonstrated a significant improvement in symptoms and decreased rates of endotracheal intubation with either modality as well as decreased mortality with the use of CPAP only. The largest randomized trial of NIV, 3CPO, however, failed to show a benefit in regard to mortality or intubation rates with either modality, although intubation rates were overall quite low. The 3CPO trial

did confirm a small but significant improvement in symptoms and surrogate markers, such as heart rate and pH. As such, non-invasive ventilation with either modality is recommended for patients with acute cardiogenic pulmonary edema for symptomatic relief. In general, patients who are younger, with lower disease acuity and only moderate derangements of oxygenation and ventilation, respond better to NIV. Contraindications to the use of NIV include facial trauma, high aspiration risk, need for emergent intubation, severely depressed mental status, and hemodynamic instability (i.e., cardiogenic shock).

HOME MEDICATIONS

When patients with chronic heart failure experience AHFS, questions often arise regarding how to manage their home medications, in particular their beta-blockers, ACE inhibitor (ACE-I)/ARB, and aldosterone therapies. Retrospective analyses of large registry and randomized control trial data have shown that beta-blocker withdrawal or dose reduction during an AHFS was associated with increased postdischarge mortality. Continuation of the outpatient beta-blocker dose was tolerated in the majority of patients. As such, in patients with congestion and preserved perfusion (see profile B in Figure 52.1), beta-blocker therapy should be continued at the outpatient dose. In patients with hypoperfusion requiring vasodilator therapy or in those whose decompensation is thought to be due to beta-blocker initiation/titration, beta-blocker dose can be decreased. In patients with hypotension or low perfusion requiring inotropic support, beta-blocker therapy should be withheld. Up-titration of beta-blocker doses should be avoided until the patient is stabilized and has achieved euvolemia. Many patients admitted with AHFS have some evidence of acute kidney dysfunction. However, ACE-I and ARBs should not be routinely withheld in this group unless a patient's kidney injury is severe or in the setting of hyperkalemia. In addition to neurohormonal blockade, ACE-I and ARBs have a significant vasodilatory effect that could help "unload" the heart and improve hemodynamics in the acute setting. Acute withdrawal can lead to increased afterload and worsening cardiac performance. Lastly, aldosterone antagonists should be withheld in any patient with hyperkalemia or acute kidney injury.

DIURETIC THERAPY

Diuretic therapy remains the cornerstone of treatment of congestion in AHFS and should be initiated in the emergency department. Loop diuretics (furosemide, bumetanide, torsemide, and ethacrynic acid) are the first-line agents (Table 52.1). In the setting of AHF, intravenous (IV) rather than oral loop diuretics should be administered given inconsistent absorption of oral medicines because of small bowel edema or hypoperfusion. Unfortunately, there are no substantial data

TABLE 52.1 ■ **Loop Diuretic Dosing**

Name	Initial Dose	Comments
Furosemide	20–80 mg IV	Can be administered as repeated bolus doses up to three times daily or as a continuous infusion (5–40 mg/h)
		Increased risk of ototoxicity with high bolus dosing (> 240 mg)
Bumetanide	0.5–2 mg IV	Continuous infusion 0.1–0.5 mg/h
Torsemide	10–40 mg po	Continuous infusion 5–20 mg/h

IV, intravenous; po, oral (by mouth).

Adapted with modification from Braunwald E, Bonow R, Mann D, et al: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Philadelphia: Elsevier Saunders, 2008.

to guide initial diuretic dosing. Typically, in patients on chronic outpatient loop diuretic therapy, the initial dose should be twice their home oral dose. In diuretic "naïve" patients, one can start with 20 to 40 mg IV furosemide (equivalent to 0.5 to 1 mg IV bumetanide or 5 to 10 mg IV torsemide). Dose increases are often required in patients presenting with renal insufficiency, as response to diuretic dosing is significantly reduced in this setting. After initiation of IV diuretics, careful monitoring of blood pressure, electrolytes, and urine output as well as daily weights should be performed and diuretic dose titrated accordingly.

Although necessary to relieve symptoms and congestion, loop diuretics are known to exert multiple deleterious effects including electrolyte depletion, volume shifts causing transient intravascular volume depletion, and activation of the neurohormonal and sympathetic nervous systems possibly leading to transient *worsening* of cardiac hemodynamics. In addition, overaggressive or excessively rapid diuresis can also result in hypotension and worsen kidney dysfunction and should be avoided. It is thus not surprising that loop diuretics and, in particular, high-dose loop diuretics have been associated in multiple nonrandomized studies with increased mortality and worsening renal insufficiency. To minimize the risk of worsening renal dysfunction, it is recommended that clinicians prescribe the smallest dose of diuretic that will create effective diuresis, monitor BUN/creatinine daily or even twice daily, avoid concomitant administration of nephrotoxic agents, and stop diuresis when the JVP has normalized or the BUN/creatinine has increased by ~25%.

DIURETIC RESISTANCE

If adequate diuresis is not achieved despite up-titration of the loop diuretic dosing, several approaches can be undertaken. The first step in an assessment of "diuretic resistance" remains assuring adequate blood pressure and perfusion (cardiac output) without which diuresis will be ineffective. If diuretic resistance is suspected, either a change in diuretic administration or the addition of another class of diuretics is warranted. Continuous IV rather than intermittent bolus infusions have been hypothesized to improve diuresis by minimizing the neurohormonal activation and by preventing the avid sodium reabsorption that occurs after the short half-life of the loop diuretic has passed. However, although meta-analyses of several smaller studies suggested a benefit to continuous infusion, a landmark randomized control trial of continuous versus bolus infusion of loop diuretics showed no statistically significantly differences between the two treatment arms. The alternate approach is the addition of a thiazide diuretic. The thiazide diuretics (metolazone, chlorthalidone, chlorothiazide) act at the distal convoluted tubule and are less natriuretic than loop diuretics. However, in patients on chronic loop diuretic therapy, the distal convoluted tubule hypertrophies resulting in increased distal sodium reabsorption. Thus, coadministration of thiazide and loop diuretics allows for a "synergistic effect" with increased natriuresis. In addition to potentiating the natriuresis of loop diuretics, thiazides also potentiate the hypokalemia, hypomagnesemia, hyponatremia, and potential renal insufficiency associated with their use, so their combined use should be carefully monitored. The addition of other potassium sparing diuretics (spironolactone, triamterene, etc.) should be reserved for patients with hypokalemia or those unresponsive to the combination diuretic therapies. Novel agents such as arginine vasopressin (AVP) receptor antagonists have been shown to have a modest effect on symptoms and diuresis, without a significant effect on mortality. Their eventual niche in management of AHFS remains to be seen.

ULTRAFILTRATION

Ultrafiltration (UF) is an alternate method for fluid removal in patients with AHF that has several theoretic physiologic benefits over diuretic therapy. Although diuretic therapy induces hypotonic diuresis, UF results in removal of isotonic and isonatremic fluid. This increases sodium removal per

liter of fluid removed and because of the isotonic fluid removal, the electrolyte abnormalities seen with diuretic therapy do not occur. In addition, although diuretic therapy induces neurohormonal and sympathetic nervous system activation, these adverse responses are not seen in patients treated with UF. Lastly, there is a theoretic benefit hypothesized that UF can remove cytokines and other inflammatory mediators that exert negative cardiac effects. From a practical perspective, UF provides both advantages and disadvantages. The principal advantage is the rapidity of fluid removal (up to 500 mL/h). The disadvantages are the need for venous access (which can now be performed via a peripheral rather than a central vein), the resultant risks of venous damage, infection, and cost.

Multiple small trials in a broad range of heart failure patients have shown that UF effectively removes volume and ameliorates patients' symptoms without negative renal effects. The largest of these trials, the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial, confirmed these findings. It showed that in acute heart failure patients without hemodynamic compromise, UF therapy resulted in greater fluid removal and decreased rates of rehospitalizations as compared to diuretic therapy without a negative effect on renal function. Currently, governing cardiology societies in Europe, the United States, and Canada state that UF can be used as a second-line modality for fluid removal if traditional therapy with diuretics and vasodilators become ineffective. Consultation with a heart failure or nephrology specialist is recommended.

VASODILATORS

There are three principal IV vasodilators used in AHFS: sodium nitroprusside, nitroglycerin, and nesiritide (Table 52.2). These vasodilators have differential effects on venous versus arterial vasodilatation but share a common mechanism of action of activating soluble guanylate cyclase in

TABLE 52.2 ■ **Intravenous Vasodilators**

Name	Initial Dose	Effective Dose Range	Comments
Nitroprusside	5–10 mcg/min	5–300 mcg/min	May be titrated quickly (every 5 minutes) until desired effect
			Doses > 400 mcg/min not recommended
			Avoid in patients with myocardial ischemia
			Can cause hypotension; recommend pulmonary artery catheter (PAC) monitoring
			Side effects: cyanide and thiocyanate toxicity
Nitroglycerin	10 mcg/min	10–400 mcg/min	May be titrated quickly (every 5 minutes) until desired effect
			Tachyphylaxis can occur within 24 hours
			Side effects: hypotension, headache
Nesiritide	0.01–0.03 mcg/kg/min*	0.01 mcg/kg/min†	Increase infusion rate by 0.005 mcg/kg/min no more frequently that every 3 hours
			Side effects: hypotension, headache

*FDA instructions recommend a bolus dose of 2 mcg/kg prior to initiation of continuous infusion; many centers forego bolus dosing because of hypotension.
†Maximum dose is 0.03 mcg/kg/min; however, limited data are available on using doses > 0.01 mcg/kg/min.
Adapted with modification from Braunwald E, Bonow R, Mann D, et al: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Philadelphia: Elsevier Saunders. 2008.

smooth muscle cell and thereby increasing intracellular cyclic guanosine monophosphate (cGMP) levels that, in turn, induce vasodilation. Vasodilator use is hypothesized to improve cardiac performance via decreasing filling pressures, afterload (see Figure 8.4 in Chapter 8), and mitral regurgitation as well as through associated decreases in neurohormonal activation. Vasodilator therapy is recommended in three scenarios: (1) profile C patients (i.e., patients with evidence of hypoperfusion and elevated filling pressure in Figure 52.1) who have an adequate blood pressure as a way to stabilize organ perfusion and transition to oral heart failure therapies; (2) patients with hypertensive AHF, typically acute cardiogenic pulmonary edema; and (3) patients with ongoing angina who are awaiting intervention.

However, two further clinical scenarios could benefit from vasodilator use but typically require invasive monitoring with a pulmonary artery catheter (PAC) for diagnosis and management. The first is in profile C (see Figure 52.1), patients with *marginal* blood pressure with a PAC revealing elevated SVR and depressed cardiac index (CI). This group of patients often responds to vasodilation with a concomitant increase in CI and maintenance of their MAP. However, without the data from the PAC to *prove* their elevated SVR, initiation of vasodilators could potentially induce hypotension and worsening cardiogenic shock. The second scenario is in patients classified as profile B (i.e., patients with evidence of elevated filling pressures and intact perfusion in Figure 52.1) who experience incomplete resolution of congestion despite diuresis and standard oral therapies. These patients labeled "diuretic resistant" can also benefit from a right heart catheterization to ensure that they are adequately vasodilated and not misclassified as profile B when they are in fact profile C.

SODIUM NITROPRUSSIDE

Sodium nitroprusside (SNP) is a short-acting vasodilator with both venodilating and arteriodilating effects, thereby decreasing both preload and afterload. Because of its rapidity of action (half-life 2 minutes), it is ideal in clinical scenarios that require urgent hemodynamic therapies such as acute aortic insufficiency, acute mitral regurgitation, aortic dissection (after initiation of IV beta-blocker therapy), and hypertensive emergencies. In AHFS, it can also be used in patients with depressed LV function with severe congestion, elevated SVR or severe mitral regurgitation. Typically, the MAP remains constant with therapy as the decrease in afterload (SVR, filing pressures) is balanced by an increase in CO (Equation 1).

However, SNP infusion, though effective, can result in multiple untoward effects, and close monitoring in an ICU setting is required. The primary concern with SNP infusion is hypotension given its effects on both preload and afterload. Invasive BP monitoring is essential, and PAC monitoring is recommended to monitor response to therapy and to aid in rapid initiation of oral therapies to allow for SNP discontinuation. In addition, SNP is metabolized to cyanide in the blood, which is subsequently processed to thiocyanate by the liver and subsequently eliminated by the kidney. To avoid cyanide toxicity, prolonged infusions of SNP (> 72 hours) should not be performed in patients with kidney or liver dysfunction. Furthermore, based on trial data, SNP should also not be infused in patients with AHF complicating AMI in the first 9 hours. Other side effects include hypoxemia in patients with chronic obstructive pulmonary disease (COPD) and coronary steal syndrome in patients with coronary artery disease (Chapter 50).

NITROGLYCERIN

Intravenous nitroglycerin has a relatively short half-life (3 to 5 minutes) and exerts a predominantly venodilating effect at lower doses with subsequent arterial vasodilation at higher doses (> 250 mcg/min). Nitroglycerin can be administered intravenously, transdermally, or sublingually, although transdermal administration is not recommended in patients with heart failure because of inconsistent absorption. Nitroglycerin can be given sublingually in patients presenting with

severe symptoms as a bridge to IV administration. Nitroglycerin is typically used in patients with or without LV dysfunction who present with coronary ischemia, mitral regurgitation, or heart failure (typically acute pulmonary edema) complicating acute hypertension. The rapid decrease in preload results in a prompt decrease in pulmonary congestion because of decreased filling pressures, without a concomitant increase in myocardial oxygen demand. Furthermore, the arterial dilation seen at higher doses extends to the coronary arteries thereby theoretically improving coronary perfusion. Given the predominant venodilatory effect of nitrates, they should be avoided in situations of preload dependence such as severe aortic stenosis, dynamic LV outflow obstruction, or RV failure. Nitroglycerin should also not be the first vasodilator of choice in patients in whom the primary target is systemic vascular resistance reduction.

Nitroglycerin therapy suffers from several significant drawbacks. The major limitation to nitroglycerin use remains tachyphylaxis, which occurs in ~20% of patients and can appear within the first 24 hours of infusion. In addition, as with SNP infusion, hypotension is a serious concern, especially in patients concomitantly prescribed phosphodiesterase-5 (PDE5) inhibitors in whom nitroglycerin administration is contraindicated. Other side effects include headache and rarely methemoglobinemia.

NESIRITIDE

Nesiritide is a recombinant form of human BNP and exerts vasodilatory effects on the venous, arterial, and coronary circulations. Although small studies have demonstrated numerous beneficial hemodynamic effects (including decreasing LV filling pressures, reducing SVR, and increasing cardiac output) without increasing HR or myocardial oxygen demand, subsequent meta-analyses showed a nonsignificant trend toward worsening renal function and mortality with its use. In 2011, the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND HF) trial, a randomized trial of more than 7000 patients, demonstrated that although nesiritide did not impact mortality or renal dysfunction, its use was associated with only mild improvement in symptoms. Not surprisingly, there was a statistically significant increase in episodes of hypotension in the treatment arm. Furthermore, as nesiritide has a longer half-life (18 minutes) than nitroglycerin or SNP, its hypotensive effects can persist for several hours. As such, nesiritide presently remains an option in AHF treatment, although its role has become more limited. It is not recommended for routine treatment in AHF but can be used in combination with diuretics in patients with adequate blood pressure (> 90 mm Hg) and symptoms of dyspnea at rest. To minimize the risks of hypotension, bolus infusions are no longer recommended and doses of continuous infusion should remain ≤ 0.01 mcg/kg/min. Careful monitoring of blood pressure, urine output, and kidney function is required.

Inotropic Therapy

Inotropic therapy, also termed inodilator therapy, improves hemodynamic parameters by increasing cardiac output, decreasing filling pressures, and reducing SVR. This favorable hemodynamic profile, however, has not translated into improved clinical outcomes. Multiple retrospective analyses have shown increased rates of hypotension, arrhythmias, and even mortality in patients treated with inotropes. Although all of the inotropes are known to cause hypotension and arrhythmias, the mechanism by which short-term inotropic therapy influences long-term mortality is poorly understood. One hypothesis is that the increased inotropy leads to increased myocardial oxygen demand, which when combined with possible hypotension results in coronary hypoperfusion and myocardial injury. This has been borne out in animal experiments and supported by post hoc analyses. As such, inotropes should *not* be routinely prescribed for patients with AHF. Rather, inotropic therapy should be reserved for patients with systolic dysfunction presenting

TABLE 52.3 ■ **Inodilator* and Vasopressor Agents Used in the Treatment of Acute Heart Failure**

Name	Initial Dose	Effective Dose Range	Comments
Inodilators			
Dobutamine	1–2 mcg/kg/min	2–20 mcg/kg/min	Tachyphylaxis Side effects: arrhythmias, hypotension, tachycardia
Milrinone	0.125–0.250 mcg/kg/min†	0.125–0.750 mcg/kg/min	Caution with renal dysfunction Side effects: arrhythmias, hypotension
Levosimendan	6–24 mcg/kg bolus followed by infusion	0.05–0.2 mcg/kg/min	Not currently approved in the United States Side effects: arrhythmias, hypotension
Vasopressor Agents			
Dopamine	1–5 mcg/kg/min	2–20 mcg/kg/min	Increasing vasoconstriction at higher doses (> 4 mcg/kg/min) Side effects: arrhythmias, tachycardia
Epinephrine	1–2 mcg/min	1–20 mcg/min	Potent vasoconstrictor at higher doses Side effects: arrhythmias, tachycardia, hypertension, end organ hypoperfusion
Norepinephrine	2 mcg/min	2–60 mcg/min	Side effects: arrhythmias, tachycardia, hypertension, end organ hypoperfusion

*Drugs that have both inotropic and vasodilating properties.
†FDA instructions recommend a bolus dose of 50 mcg/kg prior to initiation of continuous infusion; many centers forego bolus dosing because of hypotension.

with hypotension and concomitant hypoperfusion (with or without congestion—profiles L and C in Figure 52.1) who are either too hypotensive for the initiation of vasodilators or unresponsive to them. In these cases, the goals of inotropic therapy are to improve cardiovascular performance and restore organ perfusion. Although invasive hemodynamic monitoring is not required, it is recommended, especially in patients with hypotension or worsening kidney function on therapy. In a small subset of patients with cardiogenic shock who have severe hypotension, the initiation of inotropes could worsen hypotension if the vasodilatory properties of the inotropes are not offset by an increase in cardiac output. In this select group, vasopressor agents are needed, followed by the addition of inotropes. Table 52.3 describes the inodilators and vasopressor agents used for the treatment of AHF.

DOBUTAMINE

Dobutamine is the most frequently used inotrope throughout the United States and Europe. It is a nonselective beta agonist, which at low doses predominantly affects B1 and B2 receptors with a resultant increase in inotropy, chronotropy, and a decrease in SVR. At higher doses, there is stimulation of the alpha 1 receptor with resultant vasoconstriction. Dobutamine has a relatively short half-life of 2 minutes with swift onset (1 to 10 minutes) allowing for rapid dose titrations. When it is time to discontinue the dobutamine, the recommendation is to gradually lower the dose by 2 μg/kg/min rather than an abrupt cessation. Side effects include hypotension, tachycardia, arrhythmias (atrial and ventricular), and increased AV conduction resulting in faster conduction

of atrial arrhythmias. As compared with milrinone, dobutamine carries a lower risk of hypotension but likely causes a larger increase in myocardial oxygen consumption. In addition, although beta-blocker therapy can be continued concomitantly with milrinone, potentially decreasing the risk of side effects and worsening left ventricular function, they must be discontinued in patients on dobutamine, further increasing arrhythmic risk. Lastly, although dobutamine is often administered for short time intervals, there is concern for the development of tachyphylaxis, so long-term administration is not recommended.

MILRINONE

Milrinone's mechanism of action is inhibition of phosphodiesterase-3, thereby increasing cyclic adenosine monophosphate and intracellular calcium levels. This results in increased inotropy as well as peripheral and pulmonary vasodilatation. Milrinone is the only inotrope studied in a large randomized control trial in AHF. The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME -CHF) trial randomized 951 patients with AHF who were *not deemed* to require inotropic therapy to placebo versus high-dose milrinone infusion. This study showed that the routine use of milrinone infusions in patients with AHF had no beneficial effect on mortality or hospitalizations but did increase rates of hypotension and arrhythmias. In addition, retrospective analysis showed increased morbidity and mortality in the subgroup of ischemic patients. This lends further support to the concept that inotropes should not be used routinely in AHF but rather reserved for patients who require them to maintain organ perfusion. In addition, because of the hypotensive and arrhythmic side effects, many centers do not use bolus dosing and initial continuous infusion dosing should start at the lowest effective dose with some centers starting at 0.125 mcg/kg/min, a fraction of the dose used in OPTIME-CHF.

As compared to dobutamine, milrinone has a longer half-life (2.5 hours) with a longer time to onset and offset of action. In addition, there are no reports of tachyphylaxis to milrinone. The pulmonary vasodilatory property of milrinone is unique among the inodilators, and the peripheral vasodilation appears to be greater. However, as mentioned previously, the enhanced vasodilatory effect carries with it an increased risk of hypotension. Lastly, unlike dobutamine, which acts at the adrenergic receptors, milrinone's mechanism of action is distal to the receptor, so it can be administered concomitantly with beta-blocker therapy without negating milrinone's inotropic effects. This can theoretically attenuate some of the proarrhythmic effects as well as some of the longer-term myocardial injuries of milrinone.

LEVOSIMENDAN

Levosimendan is an inodilator that is currently approved in several European countries but not in the United States. Levosimendan increases inotropy via calcium sensitization in the myocyte and induces peripheral vasodilatation via activation of potassium channels in vascular smooth muscle. Levosimendan improves cardiac output, decreases filling pressures, and reduces SVR without increasing myocardial oxygen demand or activating the sympathetic nervous system. Levosimendan also improves coronary blood flow and is hypothesized to be cardioprotective by preventing myocyte apoptosis. Small early clinical trials showed improved hemodynamic parameters and mortality with levosimendan relative to placebo or dobutamine. However, larger studies have shown a trend toward increased mortality with its use relative to placebo and no substantial benefit or detriment relative to dobutamine. Relative to dobutamine, there were increased rates of atrial fibrillation, hypokalemia, headache, and agitation with lower rates of HF events. European Society of Cardiology guidelines recommend that in AHF patients with hypoperfusion and an SBP > 100 mm Hg, levosimendan can be administered with a bolus dose followed by a constant infusion. However, the bolus dose is often omitted to prevent hypotensive episodes (see Table 52.3).

VASOPRESSOR AGENTS

In patients presenting with AHF, a minority present with cardiogenic shock requiring inotropes, or even less commonly severe cardiogenic or mixed shock requiring vasopressors. As cardiac dysfunction progresses or if concomitant noncardiac processes are ongoing (e.g., sepsis), hypotension can ensue and preclude the use of inotropes. When this occurs, and hypotension becomes severe, vasopressor therapy should be instituted. In contrast to inotropic therapy where the primary goal is to augment cardiac output (with the concomitant goal of vasodilatation), the primary goal of vasopressor therapy is to increase or maintain a patient's MAP. Although the primary target of these groups of drugs is different, there is substantial overlap, as the majority of the vasopressor agents have concomitant inotropic effects. Table 52.3 describes the three vasopressors used in the treatment of AHF: norepinephrine, dopamine, and epinephrine. These agents have different receptor profiles and pharmacokinetics but share a similar common pathway of activation of beta 1 receptors resulting in increasing inotropy, chronotropy, and cardiac output in addition to their effects of vasoconstriction in the periphery. There are no substantial data to guide the use of one of the vasopressors over the other in the setting of cardiogenic shock. Two available vasopressors, phenylephrine and vasopressin (not included in Table 52.3), are pure peripheral vasoconstrictors and have no inotropic effect. As such, they should be avoided in patients with systolic dysfunction and AHF. In cardiac patients, their use should be restricted to patients with preserved or only mildly depressed ejection fractions who are hypotensive and have a contraindication to beta 1 stimulation (e.g., supraventricular or ventricular tachycardias).

Role of Invasive Hemodynamic Monitoring

The role of invasive monitoring with a PAC has been widely debated. Although several studies have shown no benefit to the *routine* use of PACs in everyone presenting with AHF, multiple clinical scenarios exist in which a PAC is needed to make the diagnosis and to guide therapy. This is reflected in the ACC/AHA 2009 guidelines that recommend invasive hemodynamic monitoring in the following situations: (1) inability to wean off inotropes despite initial positive response, (2) refractory cardiogenic shock poorly responsive to vasopressor therapy with possible need of mechanical support (discussed later) or heart transplantation, (3) patients with poor response to therapy in whom filling pressures or adequacy of perfusion cannot be reliably determined, and (4) in patients with recalcitrant symptoms despite adequate therapy. The guiding principle behind these four situations is that PAC use should be limited to situations in which the hemodynamic profile of the patient is uncertain, current treatments are ineffective, or when the severity of cardiac dysfunction is severe enough to warrant mechanical support or transplantation.

In addition to the preceding scenarios mentioned in the guidelines, insertion of a PAC should be considered in select cases when the evaluation of pulmonary artery pressures and PVR is needed. These include evaluating PVR prior to listing for heart transplantation, diagnosis of pulmonary arterial hypertension, as well as evaluating efficacy of pulmonary vasodilator therapies. Lastly, hemodynamic monitoring can also be considered for distinguishing cardiogenic from other forms of shock but is not routinely recommended unless there is clinical uncertainty that would impact management. This distinction is typically based on history and physical examination with the aid of laboratory and radiologic testing. However, not infrequently, the clinical scenario is not straightforward or multiple forms of shock coexist at which point more invasive monitoring may be warranted.



An annotated bibliography can be found at www.expertconsult.com.

Mechanical circulatory support using ventricular assist devices, extracorporeal membrane oxygenation (ECMO), or an intra-aortic balloon pump (IABP) is reserved for patients with refractory shock that is unresponsive to IV inotropes. An intra-aortic balloon pump is particularly useful for patients with ischemia who need increased coronary perfusion and for those who need afterload reduction in the setting of severe mitral regurgitation or refractory high SVR heart failure. IABP is contraindicated in severe vascular disease as well as aortic insufficiency. Short-term ventricular assist devices that can be placed percutaneously are particularly useful for patients in whom the ventricular failure is felt to be short lived or to allow for transport to a center that can place a more permanent device. The typical use for a percutaneous ventricular assist device is the patient with an acute myocardial infarction and cardiogenic shock who has been revascularized in the laboratory and needs 24 to 48 hours of support in order to recover. More permanent ventricular assist devices, including left, right, or biventricular assist devices, can be used to support a patient to recovery or transplant, and select left ventricular assist devices can be used for permanent support in lieu of cardiac transplant (Chapter 88). ECMO or cardiopulmonary bypass can be used acutely to salvage a patient in refractory shock (or electrical instability–intractable ventricular tachycardia) in order to provide end-organ perfusion. Typically this is a bridge to a more permanent ventricular assist device. ECMO can be placed percutaneously and rapidly at the bedside, catheterization laboratory, or operating room. The most important aspect of mechanical circulatory support is recognition of refractory heart failure that is unresponsive to inotropes so that support or transfer to an experienced center can be initiated before end organ dysfunction becomes too severe and irreversible.

PHASES II AND III: IN-HOSPITAL AND PREDISCHARGE PHASES

After the early phase of treatment, once vital organ perfusion has been stabilized, the goals of treatment shift toward transitioning to oral evidence-based therapies and achieving euvolemia. It is imperative to ensure that congestion has been appropriately treated, as high filling pressures are associated with neurohormonal activation, residual symptoms, and mortality. Symptoms should be evaluated at rest and, if possible, with exertion to confirm resolution. An oral diuretic regimen should be established and tried for 24 hours prior to discharge to ensure the adequacy of dosing. ACE-I and beta-blocker therapy should be initiated in all eligible patients barring contraindications (e.g., intolerance because of hypotension, acute kidney injury), as registry data have shown that initiation of these therapies prior to discharge is associated with decreased short-term mortality. Beta-blocker therapy should be initiated only after achieving euvolemia, and caution should be exercised in patients previously requiring inotropic therapy. In this latter group of patients, beta-blocker therapy should be initiated at low doses and at least 24 hours prior to discharge to ensure hemodynamic stability and tolerability. In addition, patients who had previously required milrinone therapy should not be discharged within 48 hours of its discontinuation given its long half-life. In patients with systolic dysfunction, initiation of other evidence-based therapies such as aldosterone antagonists, digoxin, combination Isordil/hydralazine, and cardiac resynchronization therapy (CRT) or implantable cardiodefibrillator (ICD) therapy should be considered on an individual basis.

Prior to discharge, the patient and family should receive education on possible precipitants of AHF and their avoidance as well as on signs and symptoms that should prompt contact with the patient's physician. Given the high rate of readmission and mortality in the 60 to 90 days postdischarge, the patient should also be scheduled for close follow-up with the health care team.

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CHAPTER 53

Hypertensive Crisis and Management of Hypertension

Melissa B. Bleicher ■ Raymond R. Townsend

Admission rates to the intensive care unit (ICU) for hypertensive crises have been declining, partly because of better-tolerated and longer-acting antihypertensive drug therapy. Hypertensive emergencies are likely to occur in patients who have abruptly stopped their antihypertensive medications, recently used sympathomimetic drugs (prescription, nonprescription, or illicit), or lost blood pressure control because of the superimposition of a secondary form of hypertension (e.g., renal artery stenosis or pheochromocytoma). This chapter presents an approach on how to assess the threat of severely elevated blood pressure and how to choose and use an initial antihypertensive agent.

Definitions

The classification of hypertension undergoes periodic review by the Joint National Committee (JNC) on Detection, Evaluation, and Treatment of High Blood Pressure. The 2003 report stratifies blood pressure values into four stages: normal, prehypertension, stage I, and stage II (Table 53.1). This report defines patients with a systolic blood pressure (SBP) > 180 mm Hg or diastolic blood pressure (DBP) > 110 mm Hg as having a "hypertensive crisis." Hypertensive crisis is further stratified to include both hypertensive urgencies and emergencies. A hypertensive *urgency* is an elevated blood pressure > 180/110 mm Hg without progressive target organ dysfunction. A hypertensive *emergency* is a blood pressure > 180/110 mm Hg in the presence of progressive target organ dysfunction, where target organs include the brain, heart, retina, and kidney. Hypertensive emergencies usually occur in the presence of blood pressure values > 200/140 mm Hg, though the point at which one develops symptoms is in part dependent on the person's baseline blood pressure. The diagnosis of hypertensive crisis differs in pregnancy, and the diagnosis and management are reviewed in detail in Chapter 72. It is important to distinguish true emergencies in which rapid blood pressure reduction is necessary from urgent hypertension in which blood pressure elevations can be treated more slowly and with oral medication alone. The diagnosis of a hypertensive emergency does not rest on blood pressure readings alone, but it also requires the concomitant impairment of underlying organ systems. Many clinical situations in which there is a severe elevation of blood pressure warrant the designation of an "emergency" (Box 53.1).

Pathophysiology and Clinical Characteristics

Acute elevations in blood pressure may occur in a normotensive individual or may complicate preexisting primary or secondary hypertension. The factors leading to an abrupt and severe rise in blood pressure are thought to include the acute and excessive elaboration of humoral substances like catecholamines and activation of the renin-angiotensin-aldosterone system, causing marked and intensive vasoconstriction. The rise in blood pressure generates mechanical stress on the blood vessel walls, causing endothelial injury, which in turn triggers activation of the coagulation

TABLE 53.1 ■ **JNC Classification of Blood Pressure**

Classification	Systolic (mm Hg)	Diastolic (mm Hg)
Normal	< 120	< 80
Prehypertension	120–139	80–89
Stage I	140 ≥ 159	90 ≥ 99
Stage II	≥ 160	≥ 100
Crisis	> 180	> 110

JNC, Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.
From The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure available at www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.htm. Accessed April 12, 2013.

BOX 53.1 ■ Hypertensive Crises*

Cardiovascular Presentations

- Aortic dissection
- Left ventricular failure
- Myocardial infarction
- Postoperative vascular or coronary artery bypass surgery
- Unstable angina

Neurologic Presentations

- Hypertensive encephalopathy
- Intracranial hemorrhage
- Subarachnoid hemorrhage
- Thrombotic stroke

Miscellaneous Presentations

- Preeclampsia or eclampsia of pregnancy
- Renovascular hypertension
- States of severe catecholamine excess
  - —Clonidine withdrawal
  - —Illicit drug use (LSD, cocaine, methamphetamine, phencyclidine)
  - —Phenylpropanolamine use
  - —Pheochromocytoma
  - —Tyramine, MAO inhibitor drug interaction

**A hypertensive crisis is the occurrence of severe hypertension with one or more of the clinical conditions listed in this table.*
LSD, lysergic acid diethylamide; MAO, monoamine oxidase.

cascade with intraluminal platelet and fibrin deposition as well as increased vascular permeability. More severe and sustained elevations in blood pressure result in fibrinoid necrosis of the arterioles, which then causes a breakdown in autoregulation at the level of the vascular beds.

AUTOREGULATION

Blood pressure represents a balance between the cardiac output and the peripheral vascular resistance. Hypertensive emergencies are usually due to a marked increase in vascular resistance. Organ

systems, in addition to responding to neural and humoral factors affecting blood flow, possess an intrinsic ability to control perfusion known as *autoregulation*. Autoregulation preserves blood flow over a wide range of blood pressure readings. This phenomenon has been most apparent clinically in the cerebral circulation (Figure 53.1). Chronic, poorly controlled hypertension shifts the lower and upper ends of the autoregulation curve rightward so that, although hypertensive patients tolerate higher blood pressures, the cerebral circulation does not adapt acutely to lower blood pressures that are easily tolerated in normotensive individuals. As a result, when neurologic symptoms result from a hypertensive emergency, it is important to lower blood pressure only by 20% to 25% from presenting levels to avoid precipitating further neurologic deterioration.

VASOSPASM

Blood vessels intrinsically constrict in response to increased pressure—that is, they exhibit *vasospasm*. This may be superseded by a striking decrease in vascular resistance in hypertensive emergencies, causing a "breakthrough" vasodilatation (the rightward end of the autoregulation curve in Figure 53.1) and giving vessels a sausage-like appearance of spasm alternating with dilatation. Vasospasm contributes to organ dysfunction by reducing blood flow. The associated vasodilatation is linked with the formation of edema, thrombus, and fibrinoid necrosis. One clinical correlate of this vascular damage is the appearance of hemorrhages, cotton-wool spots, and exudates in the retina.

VOLUME DEPLETION

Patients presenting with a hypertensive emergency are often volume depleted because of the pressure-related natriuresis. This relative hypovolemia activates the renin-angiotensin and the sympathetic nervous systems, both of which potentiate the blood pressure elevation in a vicious cycle. It is important to assess volume status carefully before perfunctorily administering diuretics in a hypertensive emergency.

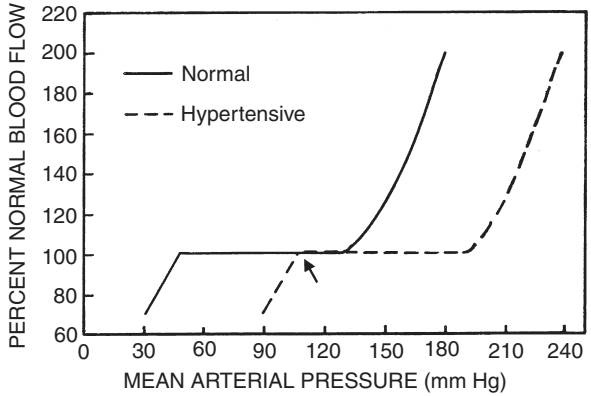


Figure 53.1 Schematic representation of autoregulation of cerebral circulation for normals *(solid line)* and chronic hypertensives *(dashed line).* Autoregulation is illustrated by the horizontal segments of each curve in which the blood flow is held constant over a range of increasing mean arterial pressure. Note that the range over which blood pressure is autoregulated is shifted to the right in chronically hypertensive patients. In these patients, decreased cerebral perfusion may result if mean arterial pressure is lowered below the takeoff of the lower "arm" of their perfusion-pressure graph *(arrow)*. *(Modified from Strandgaard S, Oleson J, Skinhoj E, et al: Autoregulation of brain circulation in severe arterial hypertension. Br Med J 1:507-510, 1973.)*

ELECTROCARDIOGRAPHIC CHANGES

In the course of rapid blood pressure reduction, one may note new electrocardiographic changes, even in the absence of known prior coronary artery disease. These changes consist of T-wave flattening or inversion and occur irrespective of the antihypertensive agent used. Although such changes may represent true ischemia, they are often attributed to a decrease in ventricular chamber size associated with rapid blood pressure reduction.

Diagnostic Evaluation

HISTORY AND PHYSICAL EXAMINATION

The evaluation of a patient presenting in a potential hypertensive crisis should be carried out quickly so that therapy can be administered promptly. Certain features in the history and physical examination can help identify hypertensive patients requiring immediate attention from those with elevated blood pressure but who are not in imminent risk of end-organ damage (Boxes 53.2 and 53.3).

The history data in Box 53.2 can help differentiate hypertensive encephalopathy (which worsens over several days) from an acute intracranial hemorrhage or thrombosis (typically with a much

BOX 53.2 ■ Recommended Questions to Ask in a Focused History in Severe Hypertension

Was antihypertensive therapy recently interrupted?
Were neurologic symptoms present?
Were they sudden (minutes to hours) or gradual (over days)?
Is there
—A severe headache?
—A visual disturbance?
—Nausea or vomiting?
Is severe dyspnea present?
Is the patient pregnant?
Does the patient have worsening angina?
Has there been any recent vascular surgery (including CABG)?
Has the patient taken sympathomimetic agents, including cold remedies, MAO inhibitors, other antidepressants, cocaine, amphetamines, or PCP?

CABG, coronary artery bypass grafting; MAO, monoamine oxidase; PCP, phencylidine.

BOX 53.3 ■ Recommended Questions to Address in a Focused Physical Examination in Severe Hypertension

Are blood pressure readings equal in both arms?
Are femoral pulses present?
Is grade III or IV retinopathy present?
Is the patient oriented to person, place, and time?
Are pupils equal?
Is the neck stiff?
Are rales or an S_3 heart sound present?
Are abdominal bruits present?
Are there focal neurologic deficits?

more acute onset with focal neurologic findings). In addition, the history may also identify clues as to why the patient has a hypertensive emergency, such as abrupt cessation of medications, the triad of paroxysmal headache, diaphoresis, and tachycardia with pheochromocytoma, or recent recreational drug use (e.g., cocaine or methamphetamine use). The physical examination can identify objective findings of organ compromise, contributing more evidence in favor of lowering blood pressure rapidly.

LABORATORY STUDIES

Additional studies that should be considered on admission include evaluation of renal function (serum creatinine, blood urea nitrogen, electrolytes, and a urinalysis with microscopy), chest radiograph, electrocardiogram (ECG), myocardial isoenzyme determination (creatine phosphokinase, troponin I) when appropriate, and plasma and urine catecholamine determinations (when pheochromocytoma is seriously suspected). A complete blood count and peripheral smear should be performed to look for microangiopathic changes in red blood cells indicating fibrinoid necrosis in the circulation (see schistocytes in Figure 45.1 in Chapter 45). One must not wait, however, to obtain the results of these tests before initiating therapy.

General Approach to Management

HOW FAST TO REDUCE BLOOD PRESSURE

After evaluation in a monitored setting (ECG and continuous or frequent intermittent blood pressure monitoring), the initial steps in reducing blood pressure pharmacologically depend on the organ system with the greatest impairment at presentation. Therapy can be initiated in many emergency departments. The "safest" level to which blood pressure can be reduced is rarely known in an individual, but empirically a 20% to 25% reduction in blood pressure is usually well tolerated.

An arterial catheter for pressure monitoring should be inserted when nitroprusside is given as a continuous intravenous (IV) infusion. Arterial catheterization is also indicated when frequent blood gas analyses are needed or if blood pressure reduction will be difficult because of lability. Importantly, patients with prior angina or known coronary artery disease or those with a history of transient ischemic attacks or carotid bruits on examination may experience symptoms related to these conditions as their blood pressure is reduced, particularly if the reduction is carried out quickly.

How fast to reduce the blood pressure depends on the clinical presentation (Box 53.1). For neurologic presentations of hypertensive crises, a gradual reduction of blood pressure over an hour or longer is indicated. For cardiovascular presentations, blood pressure should be reduced in a matter of minutes.

NEUROLOGIC PRESENTATIONS

In patients with primarily neurologic presentations (Box 53.1), it is important to avoid the use of antihypertensive drugs that may impair mental status (clonidine, methyldopa, and reserpine). Employ short-acting agents (Box 53.4) and be prepared to reduce IV drug therapy, allowing blood pressure to rise if the patient's neurologic condition deteriorates as the blood pressure is lowered. Searching for secondary forms of hypertension (particularly renovascular disease) should be postponed (but not forgotten) until the patient's clinical situation has clearly stabilized and the renal function has remained at or returned to baseline. In patients with intracranial hemorrhage or a new stroke, debate continues about whether and how much to lower blood pressure. However, the prognosis in these circumstances is poor despite therapeutic interventions. Please refer to Chapter 71 for guidelines regarding thrombolytic therapy in the management of acute stroke.

BOX 53.4 ■ Step-by-Step Guidelines for Treating Hypertensive Crises with Neurologic Changes

1. Treat diastolic blood pressure (BP) > 140 mm Hg with nitroprusside immediately (Table 53.2).
2. Wait 20 minutes for systolic BP to be > 230 mm Hg or diastolic BP to be in the 121 to 140 mm Hg range, and then give intravenous (IV) labetalol (miniboluses; see Tables 53.2 and 53.3).
3. Wait at least 1 hour to start oral therapy for systolic BP from 180 to 230 mm Hg or diastolic BP from 105 to 120 mm Hg range.
4. Do not treat blood pressures of < 180/105 mm Hg.

TABLE 53.2 ■ **Choice of Initial Agent in Hypertensive Crises**

Setting	First Choice	Second Choice	Agents to Avoid
Aortic dissection	Nitroprusside plus beta-blocker	Trimethaphan plus beta-blocker	Diazoxide, hydralazine
Catecholamine excess	Labetalol	Phentolamine (for suspected pheochromocytoma)	Selective beta-blocker
Hypertensive encephalopathy	Nitroprusside	Labetalol	Methyldopa, reserpine, clonidine
Intracranial hemorrhage with diastolic blood pressure:			
> 140 mm Hg	Nitroprusside	Labetalol, diazoxide	
121–140 mm Hg	Labetalol	Nitroglycerin	
Left ventricular failure	Nitroprusside	Nitroglycerin	Labetalol
After vascular surgery	Nicardipine	Clevidipine Nitroprusside Nitroglycerin	
Preeclampsia or eclampsia	Labetalol	Nicardipine Hydralazine	Nitroprusside, trimethaphan
Unstable angina with or without myocardial infarction	Nitroglycerin	Labetalol	Diazoxide, hydralazine

Occasionally, blood pressure falls spontaneously when these patients reach a health care setting. As a consequence, the step-by-step guidelines in Box 53.4 are recommended.

CARDIOVASCULAR PRESENTATIONS

In patients with left ventricular failure and hypertension, IV nitroglycerin and nitroprusside are both effective therapies (Tables 53.2 and 53.3), but nitroprusside usually reduces systemic blood pressure more rapidly and with better control. In patients with severe hypertension accompanying unstable angina (with or without myocardial infarction), IV nitroglycerin is considered the preferred agent, as it is associated with coronary artery vasodilatation. In this clinical setting, the "steal" phenomenon (shunting of blood away from ischemic areas by normally responsive resistance vessels, thereby worsening ischemia) has been associated with nitroprusside. The beta-blockers esmolol or labetalol (Tables 53.2 and 53.3) can be added for rate control and additional blood pressure reduction.

TABLE 53.3 ■ **Dosing of Selected Antihypertensive Agents**

Drug	Initial Dose	Maximal Dose	Onset of Action	Duration
Clevidipine	1–2 mg/h 1–2 mg should drop SBP 2–4 mm Hg	16 mg/h	2–4 min	5–15 min
Diazoxide	1 mg/kg bolus over 5 min	600 mg	< 2 min	6–12 h
Enalaprilat	1.25 mg every 6 h	5 mg every 6 h	15 min	6 h
Esmolol	0.2–0.5 mg/kg over 1 min	0.2 mg/kg/min	1–2 min	10 min
Fenoldopam	0.1 μg/kg/min	1.6 μg/kg/min	15 min	1 h
Hydralazine	10 mg	60 mg every 6 h	< 5 min	3–8 h
Labetalol bolus	20 mg over 2 min	Total of 300 mg	< 5 min	1–4 h but variable
Continuous	0.5–2 mg/min	300 mg	—	—
Nicardipine	5 mg/h	15 mg/h	< 60 min	< 1 h
Nitroglycerin	5 μg/min	100 μg/min	< 5 min	< 5 min
Nitroprusside	0.3 μg/kg/min	10 μg/kg/min	< 1 min	< 2 min

SBP, systolic blood pressure.

Specific Pharmacologic Agents (Tables 53.2 and 53.3)

DIAZOXIDE

Diazoxide is chemically related to the sulfonamide-derived diuretics of the thiazide class. When initially introduced, it was given as a 300-mg bolus and it often produced sustained blood pressure reductions that persisted for many hours. However, some patients experienced severe hypotension requiring pressor support, whereas others had worsening of angina or acute myocardial infarction. Other drawbacks to the use of diazoxide include hyperglycemia, fluid retention (requiring diuretics), and tachycardia (often requiring use of a beta-blocker). Currently, diazoxide is given as either a 1-mg/kg bolus or a 50- to 150-mg IV bolus, repeated as needed for blood pressure control. In addition, because diazoxide *increases* shear force (the change in pressure compared with the change in time [dP/dT] for the pulse wave), it should *not* be used in aortic dissection. Finally, because diazoxide increases heart rate and worsens angina, it should be avoided in unstable angina patients with or without myocardial infarction.

ENALAPRILAT

Although effective in reducing severely elevated blood pressure, IV enalaprilat is less efficacious than other available agents. Its principal usage is in hypertensive emergencies complicated by left ventricular failure.

HYDRALAZINE

Intravenous hydralazine works quickly and effectively in hypertensive emergencies. Drawbacks include worsening of coronary ischemia, usually because of a marked increase in heart rate. Thus, hydralazine is best avoided in unstable angina, myocardial infarction, or aortic dissection. There is a short latent period of ~5 to 15 minutes following IV administration of hydralazine, followed by a precipitous fall in blood pressure. The maximal effect is usually within 10 to 80 minutes

of administration, with an antihypertensive effect lasting in the range of 10 to 12 hours. In the past, hydralazine was viewed as the drug of choice in pregnancy. However, the precipitous and unpredictable drop in blood pressure may have significant deleterious effects on uteroplacental perfusion and fetal outcomes, as well as side effects that mirror those of progressive preeclampsia or eclampsia, which limit current use in favor of labetalol or nicardipine for pregnant patients.

LABETALOL

Intravenous labetalol has been used both as repeated small boluses and continuous IV infusion to treat hypertensive crisis. Labetalol has mixed beta-blocking and alpha-blocking activity. Unlike most drugs used in hypertensive crises, labetalol usually slows rather than increases the heart rate. Labetalol is contraindicated in patients in whom beta-blockade will worsen underlying conditions (see Table 53.2); IV labetalol infusion can be performed safely without an arterial line.

ESMOLOL

Esmolol is a very short acting beta-blocker that may be administered IV as both a bolus and a continuous infusion. With an elimination half-life of ~9 minutes, esmolol is metabolized by red blood cell (RBC) esterases, obviating the need for dose adjustment in renal or hepatic failure yet potentiating the duration of drug effect in the presence of anemia. The mechanism of action is reducing both heart rate and myocardial contractility, thereby decreasing cardiac output. However, unlike labetalol, esmolol has no direct vasodilatory effects. Esmolol is contraindicated in patients in whom beta-blockade will worsen underlying conditions (see Table 53.2). An arterial line is not usually necessary when using esmolol for treatment of a hypertensive emergency.

NICARDIPINE

Nicardipine is one of a few IV dihydropyridine calcium channel antagonists currently in use to treat hypertension. Nicardipine is more water soluble than other compounds in this class such as nifedipine, facilitating IV administration. Nicardipine usually does not produce sudden falls in blood pressure. The IV injection site for nicardipine, if infused peripherally, should be rotated at least once a day because phlebitis occurs frequently (~40% of patients) after 24 hours of infusion. As with labetalol, an arterial line is not usually necessary if only monitoring the antihypertensive effect of nicardipine.

CLEVIDIPINE

Clevidipine is a third-generation dihydropyridine calcium-channel blocker, approved for use in clinical settings requiring tight regulation of blood pressure. It is an ultra-short-acting arteriolar vasodilator, with a half-life of ~2 minutes. Similar to esmolol, clevidipine is metabolized by RBC esterases, obviating the need for dose adjustment in renal or hepatic failure but associated with a prolonged duration of action in the setting of anemia. Clevidipine inhibits the influx of calcium through L-type channels, thereby relaxing vascular smooth muscle of small arteries and reducing peripheral vascular resistance. Because its blood pressure-lowering effect is exclusive to the arteriole, clevidipine reduces afterload without affecting cardiac filling pressures or causing reflexive tachycardia. Most studies have focused on clevidipine use in management of hypertension during and following cardiovascular surgery, where patients reached and maintained their blood pressure targets more rapidly than with other agents with similar incidences of adverse events. This agent has not yet been studied for use in hypertensive emergencies.

BOX 53.5 ■ Principal Steps of Nitroprusside Metabolism

1. Cyanide ions (CN^-) are liberated from nitroprusside by red blood cell or endothelial cell sulfhydryl groups.
2. Cyanide ions are rapidly metabolized by rhodanese enzymes and sulfur-containing co-factors such as thiosulfate to thiocyanate (SCN^-) ions in the liver.
3. Thiocyanate ions are returned to the circulation and excreted by the kidney.
4. Hepatic disease, a lack of sulfhydry1 groups, or renal disease can impair the metabolism of nitroprusside.

NITROGLYCERIN

Intravenous nitroglycerin for hypertensive emergency has found increasing popularity in the management of unstable angina, myocardial infarction, left ventricular failure, and postoperative hypertension accompanying coronary artery bypass grafting. At low doses, venodilatory effects of IV nitroglycerin predominate; both arterial and venous dilatation occurs at increased doses.

The side effects of nitroglycerin infusion are partly related to the use of propylene glycol or ethanol as solvents. These solvents can lead to ethanol intoxication, gout, acidosis, hyperosmolality, and coma; patients with renal impairment are at greatest risk from propylene glycol. Nitroglycerin less commonly releases nitrite (NO_2^-), which serially oxidizes hemoglobin to produce methemoglobinemia, ultimately reducing oxygen transport.

NITROPRUSSIDE

In 1929, nitroprusside of sodium was found to possess antihypertensive effects. However, initial concerns over the deterioration of the compound on exposure to light and the liberation of cyanide molecules from the native chemical structure hampered therapeutic development until approval by the U.S. Food and Drug Administration (FDA) in 1974. Nitroprusside is useful in several hypertensive emergencies (see Table 53.2).

Nitroprusside Metabolism and Cyanide Toxicity

The principal steps of nitroprusside metabolism are shown in Box 53.5.

Cyanide toxicity is uncommon but should be suspected when a loss of antihypertensive efficacy (tachyphylaxis), metabolic acidosis, air hunger, confusion, headache, giddiness, or an arterial blood gas (ABG) determination with co-oximetry showing normal Pao_2 but decreased oxyhemoglobin saturation occurs. Cyanide toxicity is usually not seen at nitroprusside infusion rates < 2 μg/kg/min. One treats cyanide toxicity by infusing sodium nitrite (which induces methemoglobinemia and binds cyanide), followed by sodium thiosulfate (which facilitates the metabolism of cyanide to thiocyanate). Eli Lilly and Company markets a Cyanide Antidote Kit, which facilitates treating nitroprusside-related cyanide toxicity.

Thiocyanate Toxicity

Thiocyanate toxicity also occurs, most frequently in undialyzed patients with impaired renal function or in patients receiving high infusion rates. The manifestations of thiocyanate toxicity include tinnitus, blurred vision, delirium, anorexia, and seizures. In patients receiving nitroprusside for > 24 hours, it is prudent to monitor serum thiocyanate levels. Thiocyanate levels < 10 mg/dL (1.7 mmol/L) are well tolerated. Thiocyanate is removed by hemodialysis.

Other Cautions

1. Avoid concurrent administration of clonidine or methyldopa because fatalities from abrupt hypotension and myocardial infarction have occurred when these drugs were given concurrently with nitroprusside.
2. Discontinue infusion if the IV line becomes discolored (blue, green, or dark red).
3. Use nitroprusside with increased caution in elderly patients who are more sensitive to the drug.
4. Be aware that clinical hypothyroidism may worsen because thiocyanate inhibits the uptake and binding of iodine.

Dosing

As suggested by the FDA, a starting dose of 0.3 μg/kg per minute is recommended because of the occurrence of cyanide toxicity at the previous starting dose. Adding 10 mL of 10% sodium thiosulfate to each 100 mg (dissolved in solution) of nitroprusside reduces the risk of thiocyanate toxicity (if prolonged use of nitroprusside is anticipated) but does not cause a loss of antihypertensive efficacy.

FENOLDOPAM

Fenoldopam has been approved for short-term (up to 48 hours) management of severe hypertension. It appears to be a dopamine agonist (for the D_1 receptor) and acts as a vasodilator. Fenoldopam acts quickly and, when titrated, reaches a new balance in ~15 minutes. Administered without a bolus dose, fenoldopam appears to cause less tachycardia (the most common adverse effect noted) when the starting dose is between 0.03 and 0.1 μg/kg per minute. There is no rebound effect if the dosage is reduced or interrupted. However, fenoldopam could theoretically adversely interact with beta-blockers, with excessive hypotension possible if the rise in heart rate with fenoldopam infusion is blocked. Fenoldopam increases creatinine clearance, sodium excretion, and urinary flow rates in hypertensive patients with both normal and impaired renal function, but trials have failed to demonstrate a reduction in the need for renal replacement therapy in patients at risk for acute kidney injury. Fenoldopam causes a dose-dependent increase in intraocular pressure, and use should be avoided in patients with increased intraocular or intracranial pressures. Furthermore, the solution contains sodium metabisulfite thereby limiting its use in patients with a sulfite allergy.

Initial Therapy

Each hypertensive emergency requires its own evaluation (Tables 53.2, 53.3 and 53.4). The choice of initial agent should be guided by the relative merits of one drug over another in a specific hypertensive emergency and by the familiarity of the intensivist with each agent.

Hypertensive encephalopathy and other acute neurologic situations respond well and reliably to nitroprusside, although labetalol and nicardipine are also effective. Likewise, *left ventricular failure* in isolation responds well and reliably to nitroprusside. However, the presence of *unstable angina*, with or without *myocardial infarction*, would favor the use of IV nitroglycerin because nitroprusside may adversely affect the coronary circulation in these instances. *Dissecting aneurysms* are usually managed with nitroprusside and an IV beta-blocker (typically esmolol) to reduce aortic shearing forces. In *preeclamptic* patients, labetalol has been used successfully, although hydralazine and methyldopa are also still used. In postoperative patients, nitroglycerin, nitroprusside, or clevidipine is useful in patients who have undergone *coronary bypass* procedures, while nicardipine is useful in patients who have undergone *other vascular surgery*.

TABLE 53.4 ■ **Side Effects, Costs, and Contraindications of Selected Antihypertensive Agents**

Drug	Main Side Effect	Other Side Effects	Relative Cost*	Contraindications
Clevidipine	Hypotension	N/V, atrial fibrillation, headache	$$$$	Soy and egg allergy Defective lipid metabolism
Diazoxide	Profound hypotension	↑Heart rate, ↑glucose, N/V, flushing, sodium retention	$$	Thiazide allergy
Enalaprilat	Hypotension	Angioedema, ↑creatinine in bilateral renal artery stenosis	$$$	Angioedema
Esmolol	↓Heart rate Hypotension	Bradyarrhythmia, N/V, wheezing, headache	$$$$	Second- and third-degree AV block Sinus bradycardia Cardiogenic shock
Fenoldopam	↑Heart rate	Headache, flushing, N/V, hypotension	$$	Severe volume depletion Sulfite allergy Increased intracranial or intraocular pressure
Hydralazine	↑Heart rate	Headache, flushing, N/V	$	Angina, acute myocardial infarction, mitral stenosis
Labetalol (bolus or continuous)	Nausea	Fatigue, dizziness, scalp tingling	$$	Asthma, COPD, overt cardiac failure, more than first-degree heart block, severe bradycardia
Nicardipine	Headache	↑Heart rate, phlebitis	$$$$	Severe aortic stenosis
Nitroglycerin	Headache	↑ or ↓ in heart rate, flushing, N/V, methemoglobinemia	$	Constrictive pericardial disease
Nitroprusside	Cyanide or thiocyanate toxicity	↑Heart rate, N/V	$	Unstable angina

*Acquisition cost of drug for 24 hours at maximal dosage (approximate range: $10/day for nitroprusside versus > $200/day for nicardipine).
N/V, nausea/vomiting; COPD, chronic obstructive pulmonary disease.

Once the patient's condition has stabilized and any nausea, vomiting, or other gastrointestinal complications (such as postoperative ileus) have subsided, oral therapy should be instituted and the IV agent titrated downward.

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CHAPTER 54

Pericardial Tamponade

Scott M. Lilly ■ Steven A. Malosky ■ Victor A. Ferrari

Pericardial tamponade occurs when fluid accumulation within the pericardial space raises intrapericardial pressure to a level that impairs diastolic filling of the heart. This impairment results in elevated venous pressures and tachycardia, mechanisms that can initially maintain cardiac output. As the effusion enlarges and intrapericardial pressure continues to rise, however, cardiac output and systolic blood pressure eventually fall, and shock and death can ensue if not treated promptly. In describing the syndrome of pericardial tamponade, it is difficult to improve on the seminal description provided by Richard Lower, a 17th-century Cornish physiologist. He wrote:

> *Just as the Heart labors when affected by disease within, so it does when oppressed from without by disease of its covering. So it happens that when that same covering of the Heart is filled with an effusion, and the walls are compressed with water on every side, so that they cannot dilate to receive the blood; then truly the pulse diminishes until at length it is suppressed by even more water, when syncope, and death itself follows.*

Anatomy of the Pericardium

The heart and great vessels are surrounded by and tethered to the pericardium. The pericardium has two layers consisting of a serous membrane and a fibrous sac. The serous membrane lines the outside of the heart and proximal great vessels (visceral pericardium or epicardium) as well as the inside of the fibrous sac (parietal pericardium). The potential space between the visceral and parietal pericardium is the pericardial space. The pericardial sac is attached anteriorly to the sternum, posteriorly to the vertebral column, and inferiorly to the diaphragm. It is drained by an extensive lymphatic system by which interstitial fluid, pericardial fluid, and lymph are routed from the pericardial space to the venous system through lymphatic channels in the right pleural space and the thoracic duct.

The pericardial space normally contains between 20 and 60 mL of colorless fluid, containing 1.7 to 3.5 g/dL of protein and electrolytes in concentrations similar to serum. Pressure within the pericardial space is influenced by both intracardiac and intrapleural pressures, and it varies from −5 cm H_2O to +5 cm H_2O during a normal respiratory cycle.

Function of the Pericardium

The function of the pericardium remains a puzzle, and the congenital absence of the pericardium has no adverse effect on survival or exertional capacity. A number of roles have been suggested, including prevention of excessive dilatation of the heart, prevention of adhesions to surrounding chest structures, and maintenance of the heart in a stable geometric position within the chest. Although the pericardium does prevent distention of the heart under artificial fluid loading conditions in animals, the relevance of this to humans is questionable. An additional proposed role may be to maintain a stable diastolic coupling between the left and right ventricles over a range of hemodynamic states.

Causes of Pericardial Effusion

Fluid accumulation within the pericardial space is a prerequisite for the development of cardiac tamponade with rare exception, such as massive pleural effusions, tension pneumothorax, or pneumopericardium. Because the native pericardium is generally stiff and noncompliant, in the acute setting as little as 100 to 200 mL of fluid can cause tamponade. In the chronic setting, pericardial effusions may contain up to 2 L of fluid without tamponade, owing to slow distention of the fibrous sac. Fluid may accumulate within the pericardium as a result of infection or inflammation of the pericardium (serositis, pericarditis) or from neoplastic disorders. Iatrogenic causes include hemopericardium caused by central venous catheter perforation, a puncture of the right atrium or ventricle by a pacemaker wire, or a prior endomyocardial biopsy. Purulent pericarditis results from bacterial infection of the pericardium and is characterized by a syndrome of fever, chest pain, and a pattern often suggestive of pericarditis on the electrocardiogram. Blood or thrombus in the pericardium after trauma or thoracic surgery may also result in tamponade (Table 54.1).

Diagnosis

Tamponade should be suspected in any patient with unexplained hypotension. A change in mental status or the onset of oliguria may be early signs of systemic hypoperfusion. An enlarged cardiac silhouette on chest radiograph or changes consistent with pericarditis on the electrocardiogram (ECG) may be early clues, which, although nonspecific, should prompt the clinician to exclude tamponade as a contributing etiology.

TABLE 54.1 ■ **Differential Diagnosis of Pericardial Effusion**

Infectious	**Neoplastic**	**Connective Tissue Disease**
Viral	Metastatic spread	Systemic lupus erythematosus
Coxsackie virus	Contiguous spread	Rheumatoid arthritis
Influenza	Pericardial tumor	Sjögren syndrome
Echovirus		Scleroderma
HIV related		Whipple disease
Bacterial		Reiter syndrome
Tuberculous		Ankylosing spondylitis
Fungal		
Miscellaneous	**Cardiac Damage**	**Other Systemic Diseases**
Iatrogenic puncture of superior vena cava, right atrium, or right ventricle	Postmyocardial infarction	Uremia, chronic renal failure
	Dressler syndrome	Amyloidosis
Aortic dissection	Trauma	Hemochromatosis
Drug induced	Myocardial rupture	Myxedema
Procainamide	Post-thoracic-cardiac surgery	
Hydralazine		
Minoxidil		
Quinidine		

HIV, human immunodeficiency virus.

SYMPTOMS

Tamponade is primarily a hemodynamic diagnosis, and symptoms may be subtle, particularly at the outset. Chest discomfort is a noteworthy complaint and may be referable to pericarditis—sharp in quality and prolonged in duration. In this setting, chest pain may be relieved by the patient changing position, classically by leaning forward and worsened by lying supine. With large chronic effusions, extracardiac mechanical compression of the esophagus or the recurrent laryngeal or phrenic nerves may result in dysphagia, hoarseness, cough, or singultus (hiccupping). Once tamponade has resulted in decreased cardiac output and hypotension, dyspnea is the most common symptom and manifestations of cerebral hypoperfusion (anxiety, confusion, somnolence) may also be appreciated.

PHYSICAL EXAMINATION

Early signs of increased intra-pericardial pressure include tachycardia without hypotension and a slightly increased respiratory rate (Table 54.2). Paradoxical pulse (*pulsus paradoxus*) develops later and refers to a decline in systolic blood pressure of more than 15 mm Hg on inspiration. In the setting of tamponade the heart has a "fixed volume," such that *inspiratory-driven* increases in venous return to the right ventricle *reduce* left ventricular outflow via compression of the left *ventricle* between the septum and pericardial fluid. Though highly sensitive for cardiac tamponade, *pulsus paradoxus* is not a specific finding and occurs with other common intensive care unit (ICU) conditions such as advanced obstructive airway disease or positive pressure ventilation.

Jugular venous distention is a nearly constant finding with cardiac tamponade, but it is also evident in other conditions frequently encountered in the ICU. Although subtle, identifying the contour of the jugular venous pulse should be attempted, as the attenuation (or absence) of the y descent is an early sign of impaired diastolic filling (Figure 54.1). The heart sounds may be muffled but are usually audible, and a pericardial friction rub may be heard or palpated.

TABLE 54.2 ■ **Typical Progression of Effusion to Tamponade**

	Intrapericardial Pressure		***Hemodynamic Parameters***		
Phase	**Absolute**	**Relative**	**Heart Rate**	**Cardiac Output**	**Systemic Blood Pressure**
I. Early signs	4–8 mm Hg	< RAP	↑	Normal	Normal
II. Pretamponade	8–15 mm Hg	= RAP (↑) = RVEDP (↑) but < PAWP and < LVEDP	↑	Slightly ↓	Normal with paradoxical pulse present
III. Frank tamponade	15–30 mm Hg	= RAP (↑↑) = RVEDP (↑↑) = PAEDP (↑↑) = PAWP = LVEDP (↑↑)	↑↑	↓↓	↓↓

RAP right atrial pressure; RVEDP, right ventricular end-diastolic pressure; PAEDP, pulmonary artery end-diastolic pressure; PAWP, pulmonary artery wedge pressure; LVEDP, left ventricular end-diastolic pressure; ↑, increased; ↑↑, marked increase; ↓, decreased; ↓↓, marked decrease; =, equal; <, less than. *Note*.: These represent typical values and progression for illustrative purposes but will be affected by age, acuity of fluid collection, and comorbid conditions.

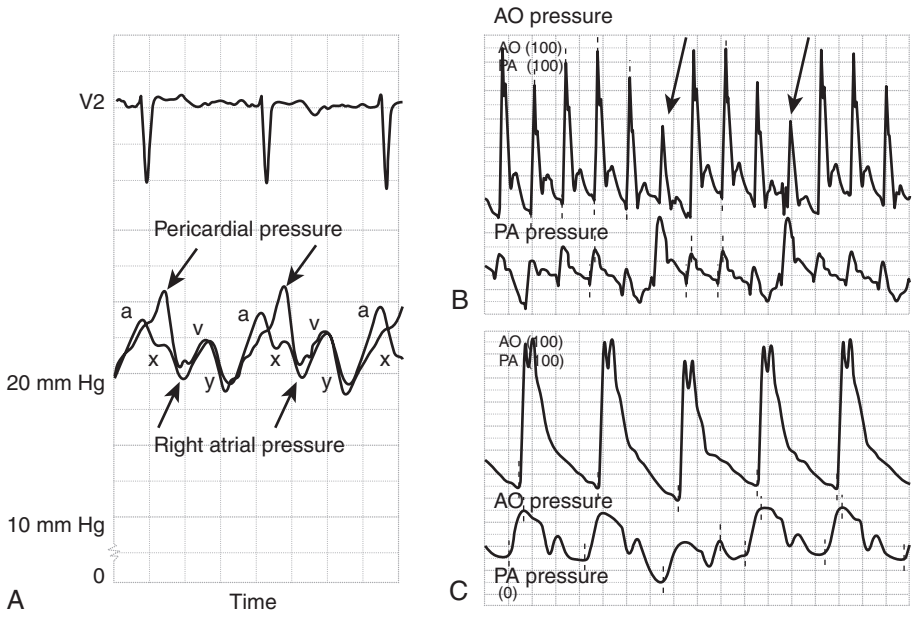


Figure 54.1 **A,** Simultaneous right atrial (RA) pressure tracing, pericardial pressure tracing *(arrows)*, and V2 lead electrocardiogram in a patient with tamponade. Note (1) increased RA pressure, (2) equalization of RA pressure with pericardial pressure (except for delayed "a" wave in pericardial pressure *[arrows]* compared to "a" wave in RA pressure), and (3) preserved "x" descent of the RA pressure tracing with attenuated "y" descent. **B,** Simultaneous aortic (AO) tracing (upper tracing) and pulmonary arterial (PA) pressure tracing (lower tracing) in the same patient prior to pericardiocentesis. Note (1) tachycardia, (2) inspiratory decrease in peak aortic pressure and coincident increase in peak pulmonary arterial pressure *(arrow),* and (3) discordant respirophasic changes in pulse pressure amplitude in aortic and pulmonary arterial (PA) pressures *(arrows).* **C,** Same patient after pericardiocentesis, without tachycardia, and concordant normal respirophasic changes in aortic (upper tracing) and pulmonary arterial (lower tracing) pressure waveforms.

ELECTROCARDIOGRAPHY

A large pericardial effusion may cause low voltage on the ECG, defined as less than 5 mV absolute voltage for the QRS complex in the limb leads (I, II, III, aVF, aVL, and aVR) or 10 mV in the precordial leads (V1 to V6; Figure 54.2*B*). In the individual patient, however, it is usually more helpful to compare the current electrocardiogram amplitude to prior tracings.

If pericarditis is present, characteristic electrocardiographic findings may be apparent (Figure 54.2*A*). *PR segment depression* is best appreciated in leads II, aVF, and V_3 through V_6. In contrast, lead aVR usually shows PR elevation. *Diffuse ST segment elevation* may mimic acute myocardial infarction to the untrained eye, though it is distinguishable by its diffuse distribution and upward concavity. Reciprocal ST depression is generally seen in lead aVR. *T-wave inversion* is a variable finding. A less common finding in the setting of pericardial effusion is "electrical alternans," in which the amplitude of the QRS complex alternates from beat to beat or in a periodic manner. This reflects rhythmic changes in cardiac position and consequent changes in the QRS axis, occurring most commonly with large pericardial effusions (see Figure 54.2*B*).

CHEST RADIOGRAPHY

Although the cardiac silhouette is commonly enlarged in the presence of a large pericardial effusion, the absence of an enlarged silhouette does not exclude the diagnosis of tamponade. This

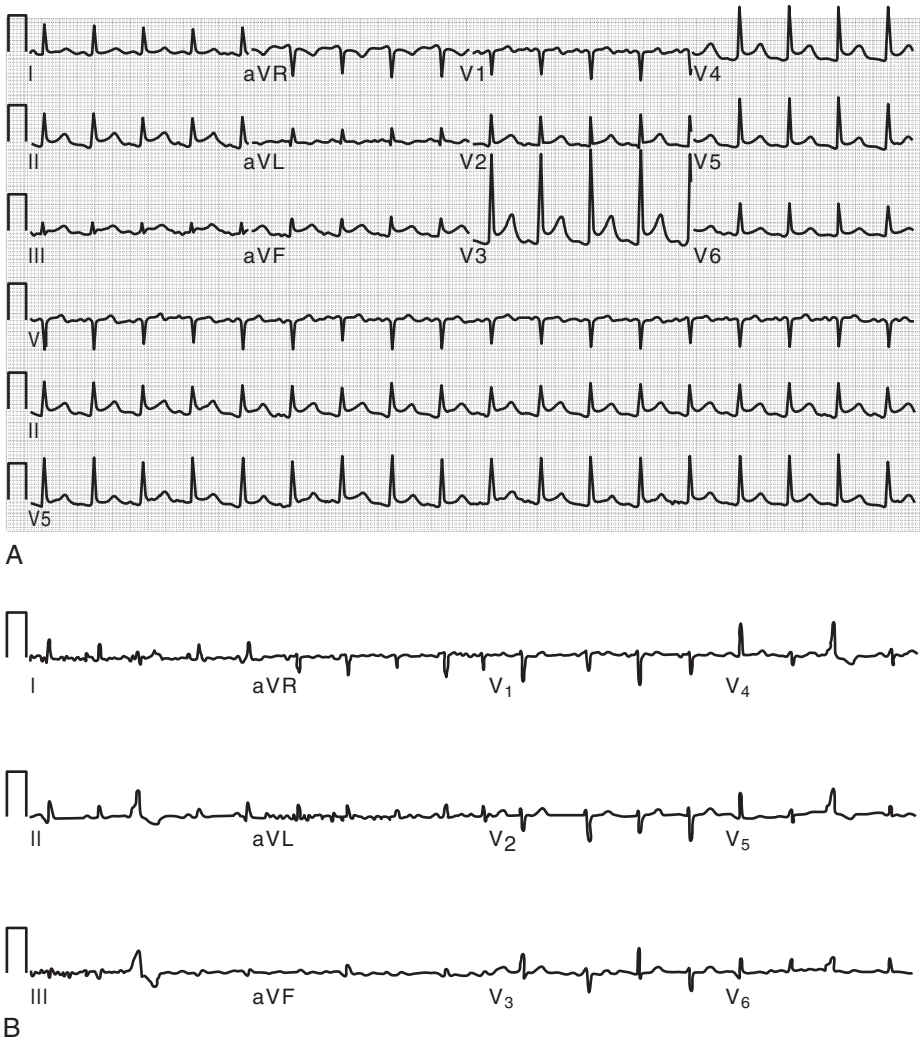


Figure 54.2 **A,** Electrocardiogram (ECG) in acute pericarditis. Note concave upward, diffuse ST segment elevation and PR depression (except in aVR, which shows the opposite changes). The upright T waves denote the acute phase of pericarditis. **B,** ECG in large pericardial effusion. Note also the low-amplitude QRS voltage in the limb leads and the alternation in the QRS axis characteristic of a large associated effusion.

is because the volume of pericardial fluid (or thrombus) causing tamponade may be small if it accumulates rapidly or after chest surgery. The presence of a large pleural effusion should be noted because it alone may cause tamponade physiology via external compression of the heart. A widened mediastinum may reflect an aortic dissection, which can rupture into the pericardial space with ensuing tamponade. A nodule in the lung field or the absence of a breast as a result of prior mastectomy may suggest the source of a metastatic neoplastic effusion. Similarly, a severe pneumonia may be the source of an infected pericardial effusion. It is also important to note the position of any central venous catheters or transvenous pacemaker wires because their unanticipated migration through the superior vena cava, right atrium, or right ventricle may cause a hemopericardium.

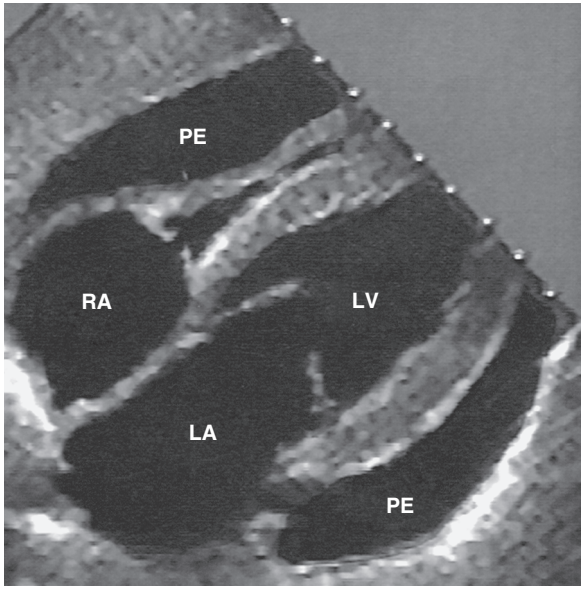


Figure 54.3 Two-dimensional echocardiographic subcostal four-chamber view of the right atrium (RA), left atrium (LA), left ventricle (LV), and a large circumferential pericardial effusion (PE) located anterior to the RA and posterior to the LA and LV. Note the mitral valve leaflets in the open (diastolic) position and the collapsed right ventricle immediately to the right of the RA, indicative of the intrapericardial pressure exceeding the RV diastolic pressure.

ECHOCARDIOGRAPHY

The echocardiogram is the single most important study in the course of evaluating tamponade, and should be obtained urgently when the diagnosis is in question. The study can usually be obtained relatively quickly, can corroborate or exclude tamponade as the provocateur of hypotension, and is invaluable for the determination of suitability for the safe performance (or guidance) of pericardiocentesis. The most obvious finding on echocardiography is the presence of increased pericardial fluid, though it need not be a particularly large or circumferential collection (Figure 54.3). Similarly, a large effusion does not clinch the diagnosis, and corroborative findings must be present. De facto tamponade is distinguished from a simple effusion by three core features: (1) atrial or right ventricular diastolic collapse, (2) the absence of a normal inspiratory decrease in the size of the inferior vena cava, and (3) exaggerated respirophasic variation in Doppler flow velocities across the atrioventricular valves (see Figure 54.3).

Clinical situations in which some of the usual echocardiographic findings of tamponade (diastolic collapse of the right-sided heart chambers) may be masked are acute or chronic pulmonary hypertension, right ventricular (RV) failure or infarction (with increased right ventricular end diastolic pressure [RVEDP]), and after cardiac surgery (because of tethering of the right side of the heart anteriorly to the sternum). The skilled observer will be alert to left atrial or left ventricular diastolic collapse in the setting of elevated right atrial (RA) and RV pressures.

PULMONARY ARTERY (SWAN-GANZ) CATHETERIZATION

Many critically ill patients have pulmonary artery (PA) catheters in place, which can be helpful in establishing a diagnosis of tamponade (Figure 54.4). As a practical point, one should make sure that the pressure tracings obtained from the PA catheter are accurate by reconfirming the zero level of the transducer and then examining the tracing carefully in the event it is overly damped or flattened. Pressure measurements should always be obtained at end expiration, and care should be taken to recognize this phase of the pressure tracing in patients on positive pressure ventilation

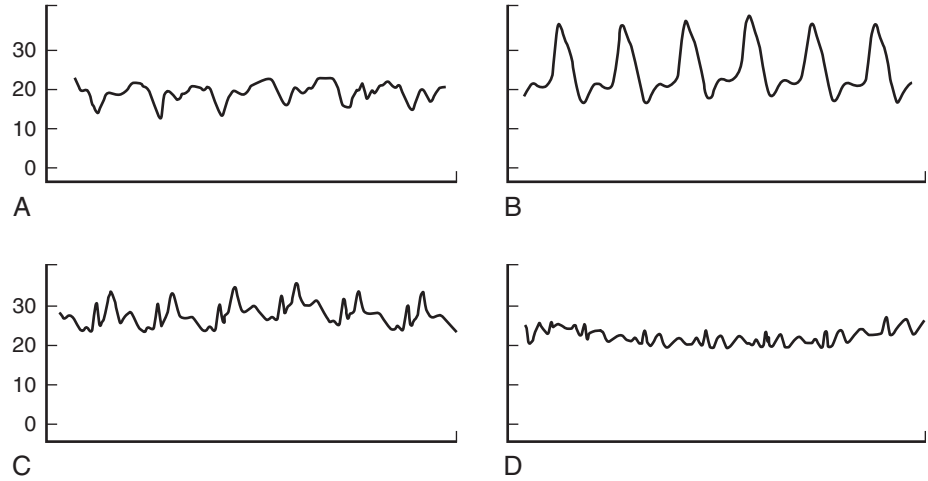


Figure 54.4 Representative hemodynamic tracings obtained by use of a Swan-Ganz catheter in a patient with cardiac tamponade. **A,** Right atrial (RA) pressure. **B,** Right ventricular (RV) pressure. **C,** Pulmonary artery (PA) pressure. **D,** Pulmonary artery wedge pressure (PAWP). Note that there is equalization of the mean RA, RV, and PA end-diastolic pressures and the mean PAWP.

(e.g., by printing out the PA pressure tracing along with a tracing of transduced airway pressure [see Chapters 7 and 11] with a two-channel recorder/printer).

The hallmark of pericardial tamponade is the elevation of diastolic filling pressures within all cardiac chambers and equalization among these pressures and those within the pericardium. Because the left ventricular end diastolic pressure (LVEDP) cannot be measured directly with a pulmonary artery catheter, pulmonary artery wedge pressure (PAWP) is used, and, in the absence of mitral stenosis, accurately reflects LVEDP. The effects of respiration on intra- and extracardiac hemodynamics are also revealing, because whereas diastolic pressures remain similar among cardiac chambers throughout the respiratory cycle, there is discordance between right and left ventricular outflow, manifest as the *pulsus paradoxus* identifiable with sphygmomanometry or on invasive arterial blood pressure monitoring (see Figure 54.1). In addition to these characteristics, more subtle changes in the RA pressure waveform are supportive of tamponade, namely an accentuated *a* wave and blunted *y* descent that collectively reflect reduced passive diastolic filling of the right ventricle and the dependence of its filling on atrial systole. Reduced cardiac output is typically a late finding, though it may occur earlier if tachycardia or increased contractility is blunted as a result of comorbid conditions or pharmacotherapies.

ADJUNCTIVE IMAGING STUDIES

If metastatic disease is suspected, computed tomography or magnetic resonance imaging of the chest and lungs may be useful in evaluating lung masses or bony lesions or detecting mediastinal lymphadenopathy. Occasionally, tumors may present with invasion of the pericardium or cardiac chambers, and either of these imaging techniques can document their presence and extent.

DIFFERENTIAL DIAGNOSIS OF TAMPONADE

Several common disorders can mimic tamponade in the ICU setting, including right ventricular infarction (see Chapters 8 and 50), major pulmonary embolism (see Chapter 77), tension

TABLE 54.3 ■ **Causes Mimicking Pericardial Tamponade**

Etiology	Hypotension, Tachycardia	Hypoxemia	Jugular Venous Pressure	Electrocardiogram	Echocardiography
Pericardial tamponade	Prominent	Not prominent	Elevated	Low voltage, occasional ST changes (see Figure 54.2)	Pericardial effusion, paradoxical inflow pattern (see Figure 54.3)
RV infarction	Prominent	Not prominent	Elevated	RV infarction pattern*	Dilated and hypokinetic RV
Massive pulmonary embolism	Prominent	Prominent	Elevated	Occasional RV strain pattern†	Dilated and hypokinetic RV
Tension pneumothorax	Prominent	May be prominent	Elevated	Decreased voltage	Shifted heart and mediastinum
Severe auto-PEEP (ventilated patients)	Prominent	May be prominent	Elevated	Decreased voltage	Frequently difficult study; underfilled LA and LV

*Typically in the setting of inferior myocardial infarction (ST elevation in leads II, III, aVF); RV involvement indicated by ST elevation in right-sided chest leads (V_3R or V_4R).
†Prominent S wave in lead I, and Q wave with T wave inversion in lead III.
RV, right ventricle; LA, left atrium; LV, left ventricle; PEEP, positive end-expiratory pressure.

pneumothorax (see Chapter 35), severe auto–positive end-expiratory pressure (auto-PEEP) (see Chapter 2), or primary or metastatic tumor involvement. All may present with dyspnea, tachycardia, jugular venous distention, and hypotension or shock (Table 54.3).

Therapy

Once the diagnosis of pericardial tamponade has been established, prompt removal of pericardial fluid should ensue. Medical therapy alone is ineffective, and intravenous (IV) fluid administration is an important but temporizing measure. Options for fluid removal include percutaneous needle drainage or open drainage via a pericardial window (performed by a cardiothoracic or thoracic surgeon). Decisions about which type of approach to use are often based on availability and local expertise rather than on controlled clinical trials. Recurrent or persistent effusions after percutaneous drainage generally require a surgical solution for sustained relief.

PERCUTANEOUS APPROACH (PERICARDIOCENTESIS)

Pericardiocentesis can be a relatively high-risk procedure if not carried out under controlled conditions. If time and resources permit, It should be performed in the catheterization laboratory and is safest when there is 1 cm or more of anterior-circumferential freely flowing pericardial fluid. With the patient positioned in a semi-upright position, a pericardiocentesis needle (18-gauge, 5 to 7 cm in length) is inserted one fingerbreadth below the xiphoid process and directed toward the midleft clavicle at a 30- to 45-degree angle from the chest wall. Complication rates generally range from 4% to 10% depending on the series and include laceration of the right atrium, right ventricle, or coronary artery; ventricular arrhythmias; laceration of the stomach, lung, or liver; pneumothorax; a major

vagal reaction; and death. Pericardial effusions that are posterior, loculated, highly fibrinous, or are the result of thrombus cannot reliably be drained percutaneously. Effusions that have recurred after a recent pericardiocentesis should generally be drained surgically.

When the cause of the effusion is unknown, pericardial fluid should be sent for cytology examination, Gram staining and routine bacterial culture, fungal culture, smear and culture for acid-fast bacilli, and determination of total protein and lactate dehydrogenase. In addition, the following laboratory studies are potentially useful in an otherwise unexplained effusion: blood urea nitrogen and serum creatinine, thyroid function tests, blood cultures (when appropriate), antinuclear antibody and rheumatoid factor, purified protein derivative (PPD) skin test and anergy panel, sputum for acid-fast bacilli smear and culture, and human immunodeficiency virus (HIV) serologic tests. In addition, if there is particular concern for a specific virus, serologic tests for coxsackievirus, echovirus, or *Mycoplasma* are available.

Conclusion

The accurate detection of pericardial tamponade requires an astute clinician and a systematic diagnostic approach. With the widespread availability of bedside echocardiography and the infrastructure for the provision of safe pericardiocentesis, this life-threatening disorder may be promptly identified and successfully treated with favorable short-term outcomes. The subsequent management of pericardial tamponade then becomes more protracted, as the etiology of the effusion frequently often has a greater bearing on subsequent patient course.

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CHAPTER 55

Hypothermia and Hyperthermia

C. Crawford Mechem

Hypothermia and hyperthermia are potentially fatal emergencies caused by environmental exposure, underlying disease processes, or drugs. Although therapy is often initiated in the prehospital setting or emergency department, multiple organ system involvement often necessitates intensive care unit (ICU) management.

Hypothermia

Hypothermia is defined as a core temperature less than 35° C (95° F). It is categorized as *mild* if core temperature is 32° to 35° C (89.6° to 95° F), *moderate* at 28° to 32° C (82.4 to 89.6° F), or *severe* at less than 28° C (82.4° F).

PATHOPHYSIOLOGY

Body temperature reflects the balance between heat production and heat loss. The four physiologic mechanisms of heat *loss* are evaporation, convection, radiation, and conduction. Conduction is enhanced by exposure to water, which increases thermal conductivity 20- to 30-fold. In response to cold stress, the hypothalamus attempts to stimulate heat production through shivering and increasing thyroid, catecholamine, and adrenal activity. Vasoconstriction simultaneously minimizes heat loss in hypothermic patients.

CLINICAL MANIFESTATIONS

As the hypothermic patient's compensatory mechanisms are overwhelmed, temperature-dependent physiologic changes occur. Patients with *mild hypothermia* demonstrate tachypnea, tachycardia, ataxia, dysarthria, impaired judgment, shivering, and diuresis. *Moderate hypothermia* is characterized by decreased pulse and cardiac output, hypoventilation, central nervous system depression, hyporeflexia, decreased renal blood flow, and loss of shivering. Atrial fibrillation and other arrhythmias may be seen. The electrocardiogram may manifest an Osborn or J wave (Figure 55.1); this secondary wave follows the S wave, most prominently in leads aVL, aVF, and $V_{1–6}$. In *severe hypothermia*, coma, hypotension, pulmonary edema, oliguria, areflexia, bradycardia, ventricular arrhythmias, and asystole occur. Ventricular fibrillation is the most common fatal arrhythmia, as hypothermia lowers the heart's fibrillation threshold. The differential diagnosis for hypothermia and predisposing factors are shown in Box 55.1.

The diagnosis of hypothermia depends on the use of a low-reading electronic thermometer to determine core temperature. It is important to know the low limit of the thermometer being used, as it is possible for the patient's temperature to be lower than the device's lowest reading. After making the diagnosis, laboratory evaluation should be undertaken to identify potential complications. Characteristic findings are presented in Table 55.1.

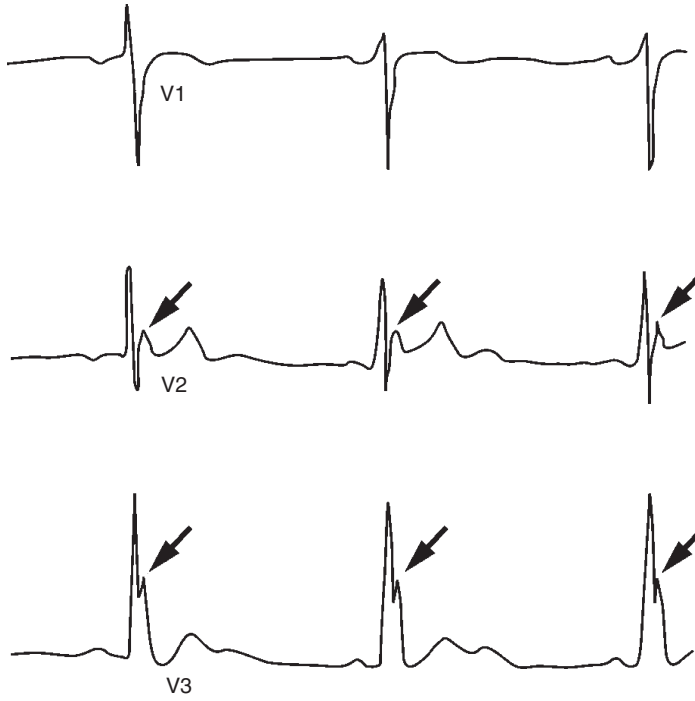


Figure 55.1 Precordial electrocardiographic leads illustrating the Osborn or "J" wave *(arrows)* in a hypothermic patient. *(Courtesy of Behzad B. Pavri, M.D.)*

BOX 55.1 ■ Differential Diagnosis for Hypothermia

Central Nervous System Disorders

Head trauma
Stroke
Wernicke's encephalopathy

Drugs

Ethanol
Phenothiazines
Sedative hypnotics

Environmental Exposure (prehospital, operating room)

Endocrine and metabolic disorders
Hypoadrenalism
Hypoglycemia
Hypopituitarism
Hypothalamic disease
Hypothyroidism
Malnutrition
Hemorrhage with massive transfusion

Medical or Surgical Acute Disorders

Pancreatitis
Sepsis
Stroke
Uremia
Iatrogenic (overshoot in cooling heat stroke victims)
Diffuse exfoliative dermatitis

MANAGEMENT

The management of hypothermia starts by stabilizing the airway, breathing, and circulation. It also includes preventing further heat loss, initiating rewarming, and treating complications (Figure 55.2). Early endotracheal intubation facilitates clearing of secretions produced by cold-induced bronchorrhea in patients with altered mental status or a decreased gag reflex. Blood pressure may

TABLE 55.1 ■ **Laboratory, Electrocardiographic, and Radiographic Findings in Hypothermia**

Tests	Findings
Arterial blood gas determination*	Metabolic acidosis, respiratory alkalosis, or both
Amylase determination	Increase caused by hypothermia-induced pancreatitis
Chest radiograph	Aspiration pneumonia, vascular congestion, pulmonary edema
Electrocardiogram	Prolongation of PR, QRS, QT intervals; ST segment elevations; T-wave inversions; Osborn J wave; atrial fibrillation or sinus bradycardia
Electrolytes	No consistent abnormality
Glucose	Increase, decrease, or no change
Hemoglobin, hematocrit	Increase caused by hemoconcentration
PT, PTT	Increase caused by inhibition of coagulation cascade
Platelet count	Decrease caused by splenic sequestration
WBC count	No consistent abnormality

*Instruments routinely perform arterial blood gas analyses on samples heated to 37° C and report results as of 37° C irrespective of the patient's temperature.
PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cell.

be supported by crystalloid infusions. Dopamine administration should be considered in cases refractory to volume resuscitation. Core temperature should be monitored closely during therapy to prevent iatrogenic worsening of hypothermia or overshoot hyperthermia.

Rewarming techniques are divided into passive external rewarming, active external rewarming, and active internal rewarming. *Passive external rewarming* is the method of choice for *mild* hypothermia. After wet clothing is removed, blankets or other types of insulation are applied, allowing the patient's intrinsic heat production to generate passive warming. This process requires sufficient physiologic reserve to generate heat by shivering or increasing metabolic rate.

Active external rewarming techniques provide heat to the patient directly. These include warm blankets, heating pads, radiant heat, or warm baths directly to the patient's skin. These methods are indicated for moderate to severe hypothermia or for patients with mild hypothermia who lack physiologic reserve, are unstable, or fail to respond to passive external rewarming. A risk of active external rewarming is *core-temperature afterdrop.* This complication occurs when the extremities and trunk are warmed simultaneously. As extremities are rewarmed, cold, acidotic blood that has pooled in the vasoconstricted extremities of the hypothermic patient flows into the core circulation, causing a drop in core temperature. This can be avoided by rewarming the trunk before the extremities by active internal warming.

Active internal rewarming is the most aggressive therapeutic strategy and may be used alone or combined with active external rewarming in moderate or severe hypothermia. Effective techniques include pleural and peritoneal irrigation with warm saline, continuous arteriovenous or conventional hemodialysis, the use of endovascular warming devices, and cardiopulmonary bypass. Giving humidified, inspired gas; warm intravenous fluids; and bladder or gastrointestinal irrigation with warm saline is adjunctive.

The hypothermic heart is sensitive to movement; rough handling, especially of the severely hypothermic patient, may precipitate *arrhythmias*. This becomes more likely at core temperatures less than 30° C (86° F). Although atrial fibrillation or flutter often resolves spontaneously with rewarming, management of ventricular arrhythmias may be problematic. The administration of

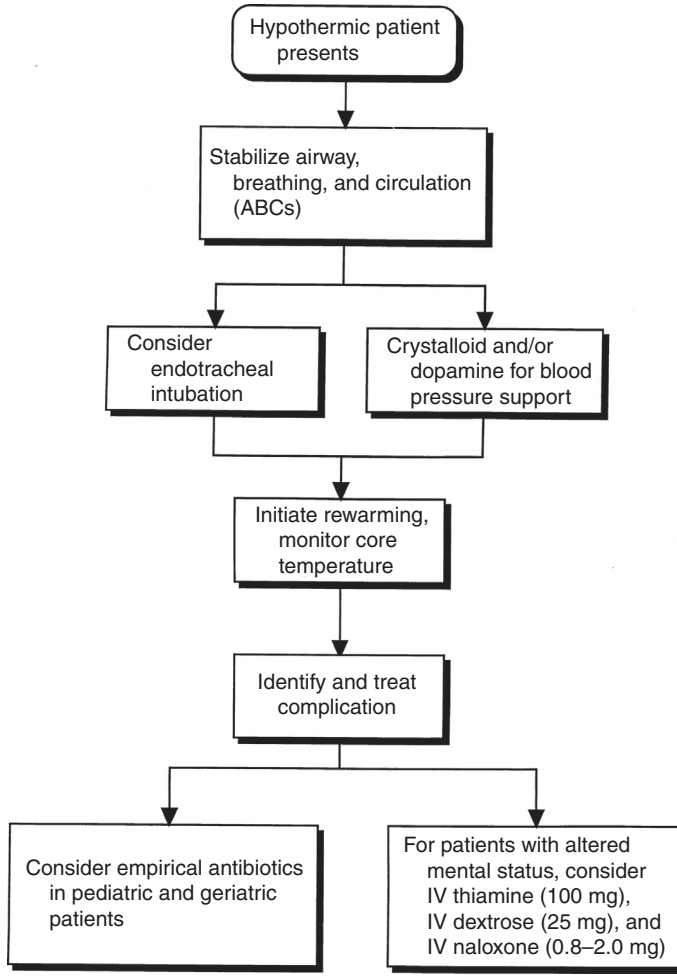


Figure 55.2 Schematic flow diagram outlining management of the hypothermic patient.

Advanced Cardiac Life Support (ACLS) medications in this setting is controversial, as ventricular arrhythmias and asystole may prove refractory until the patient has been rewarmed to a core temperature greater than 30° C (86° F). Hypothermic patients in cardiac arrest should receive defibrillation and a first bolus of the appropriate medications as indicated. However, if unsuccessful, cardiopulmonary resuscitation and aggressive rewarming must be initiated promptly. Further efforts at resuscitation should be attempted once the core temperature is 30° C and continued until the temperature is 32° to 35° C.

Hyperthermia

Hyperthermia may be defined as an elevation of body temperature to greater than the normal diurnal range of 36° to 37.5° C resulting from failure of thermoregulation. The causes of severe hyperthermia (core temperature > 40° C [104° F]) in ICU patients are heat stroke, neuroleptic malignant syndrome (NMS), and, rarely, malignant hyperthermia.

Heat stroke is defined as body temperature greater than 40.5° C (104.9° F) with associated dysfunction of the central nervous system in the setting of an excessive environmental heat load. There are two types of heat stroke: *exertional* and *classic*. *Exertional heat stroke* generally occurs in young, otherwise healthy individuals who engage in heavy exercise during periods of high ambient temperature and humidity. *Classic heat stroke* affects individuals with underlying chronic medical conditions that either impair thermoregulation or prevent them from leaving the hot environment or both.

NMS is an idiosyncratic reaction to both typical and atypical antipsychotic agents. It is characterized by hyperthermia, altered mental status, autonomic dysfunction, and muscle rigidity. NMS may mimic sepsis syndrome, including hypotension and anion gap metabolic acidosis.

Malignant hyperthermia is a rare autosomal dominant disorder precipitated by exposure to anesthetic agents, most commonly succinylcholine and inhalational agents such as halothane. Malignant hyperthermia presents as a hypermetabolic state with tachycardia, metabolic and respiratory acidosis, severe hyperthermia, and muscle rigidity.

PATHOPHYSIOLOGY

The body's heat load results from its metabolic processes plus heat absorbed from the environment. In response to rising ambient temperature, the anterior hypothalamus stimulates efferent fibers of the autonomic nervous system to produce sweating and cutaneous vasodilation. Evaporation is the principal mechanism of heat loss in a hot environment but becomes ineffective when the relative humidity is greater than 75%. Convection, conduction, and radiation play lesser roles.

In heat stroke, the body is unable to dissipate the excess heat load, and a dangerous increase in core temperature results. When the temperature is greater than 42° C (107° F), oxidative phosphorylation becomes uncoupled and enzymes cease to function. Hepatocytes, vascular endothelium, and neural tissue are most sensitive to these effects, but all organ systems may be adversely affected.

NMS is believed to result from an acute reduction of central nervous system dopaminergic transmission, caused by either dopamine receptor blockade or withdrawal of dopaminergic agonists. The frequency of NMS is directly related to the antidopaminergic potency of the neuroleptic agent. Although haloperidol appears to be the most common cause, all neuroleptic agents may cause this disorder, even when used to treat nausea. Hyperthermia results from increased muscle activity and altered hypothalamic thermoregulation.

Malignant hyperthermia results from the uncontrolled efflux of calcium from the sarcoplasmic reticulum into the cytosol, mediated by mutations in the ryanodine receptor or other calcium channels, with an associated increase in muscle activity.

The differential diagnosis for hyperthermia is extensive and includes infectious, endocrine, central nervous system, and toxic causes (Table 55.2). The diagnosis of heat stroke, NMS, or malignant hyperthermia is based on a careful history and physical examination of a patient with severe hyperthermia. The context in which symptoms develop usually suggests the cause. Rectal or core temperature should be determined in all patients. Severely hyperthermic patients may manifest sinus tachycardia, tachypnea, and hypotension or normal blood pressure with a widened pulse pressure.

Physical findings in *heat stroke* include cutaneous vasodilation, rales caused by noncardiogenic pulmonary edema, excessive bleeding resulting from disseminated intravascular coagulation, and evidence of central nervous system dysfunction such as altered mental status and seizures. The skin may be moist or dry, depending on underlying medical conditions, hydration status, and the speed with which the heat stroke developed.

NMS may present with diaphoresis, autonomic instability, muscle rigidity, fluctuating mental status, choreoathetosis, and tremors. *Malignant hyperthermia* is characterized by core temperatures up to 45° C (113° F) and muscle rigidity. The onset of malignant hyperthermia is usually within 1 hour of general anesthesia administration but may rarely present postoperatively.

TABLE 55.2 ■ **Differential Diagnosis of Hyperthermia**

Environmental exposure	Hypothalamic stroke
Sepsis	Status epilepticus
Encephalitis	Cerebral hemorrhage
Brain abscess	Neuroleptic malignant syndrome (NMS)
Meningitis	Alcohol, sedative-hypnotic withdrawal
Tetanus	Salicylate, lithium toxicity
Typhoid fever	Sympathomimetic toxicity
Thyroid storm	Anticholinergic toxicity
Pheochromocytoma	Dystonic reaction
Catatonia	Serotonin syndrome
Parkinsonism-hyperpyrexia syndrome	Malignant hyperthermia

No laboratory finding is pathognomonic. However, such studies can be used to exclude other diagnoses and screen for possible complications. Baseline studies should include a complete blood count and prothrombin and partial thromboplastin times because of the risk of disseminated intravascular coagulation, as well as electrolyte, blood urea nitrogen, and creatinine determinations; urinalysis; and measurement of creatine phosphokinase levels because of the possibility of rhabdomyolysis. Liver function tests should be performed in the setting of heat stroke. Toxicologic screening may be indicated if a medication effect is suspected. A chest radiograph may demonstrate pulmonary edema, whereas an electrocardiogram may reveal evidence of heat-related myocardial damage. A head computed tomographic scan and lumbar puncture should be considered to assess central nervous system causes.

Management of heat stroke, NMS, and malignant hyperthermia requires rapid cooling while stabilizing respiration and circulation and treating complications (Figure 55.3). Continuous core temperature monitoring with a rectal or esophageal probe is mandatory, and cooling measures should be stopped once a temperature of 39° to 39.5° C has been achieved to reduce the risk of iatrogenic hypothermia. In cases of suspected NMS or malignant hyperthermia, the potential offending agents must be stopped immediately.

Several cooling techniques exist and are the most effective for victims of heat stroke. Cold water immersion is considered the gold standard, but this is impractical when managing a critically ill patient who requires invasive procedures and constant monitoring. Evaporative cooling is therefore the modality of choice because it is effective, non-invasive, and easily performed. The naked patient is sprayed with a mist of lukewarm water while air is circulated with large fans. Resultant shivering may be suppressed with intravenous benzodiazepines or with chlorpromazine (25 to 50 mg intravenously unless NMS is suspected). Applying ice packs to the axillae, neck, and groin is effective but poorly tolerated in the awake patient. Cold peritoneal lavage is rapid but contraindicated in pregnant patients or those with previous abdominal surgery. Cold humidified oxygen, cold gastric lavage, cooling blankets, and cold intravenous fluids are adjunctive. Because heat stroke victims may be euvolemic or hypovolemic, their fluid status should be carefully assessed before aggressive fluid resuscitation is considered.

In NMS, cooling techniques may be supplemented by pharmacologic treatments. Drug therapy in NMS includes benzodiazepines; the dopamine agonist, bromocriptine, 2.5 to 7.5 mg orally every 8 hours; and dantrolene, 0.8 to 3 mg/kg intravenously every 6 hours (up to 10 mg/kg/24 h). Dantrolene is a nonspecific skeletal muscle relaxant that blocks the release of calcium from the sarcoplasmic reticulum. Although the efficacy of these agents has not been demonstrated in controlled trials, the results of several case reports suggest benefit from their use. Nitroprusside used to treat hypertension in NMS has been demonstrated to facilitate cooling by means of cutaneous vasodilation.

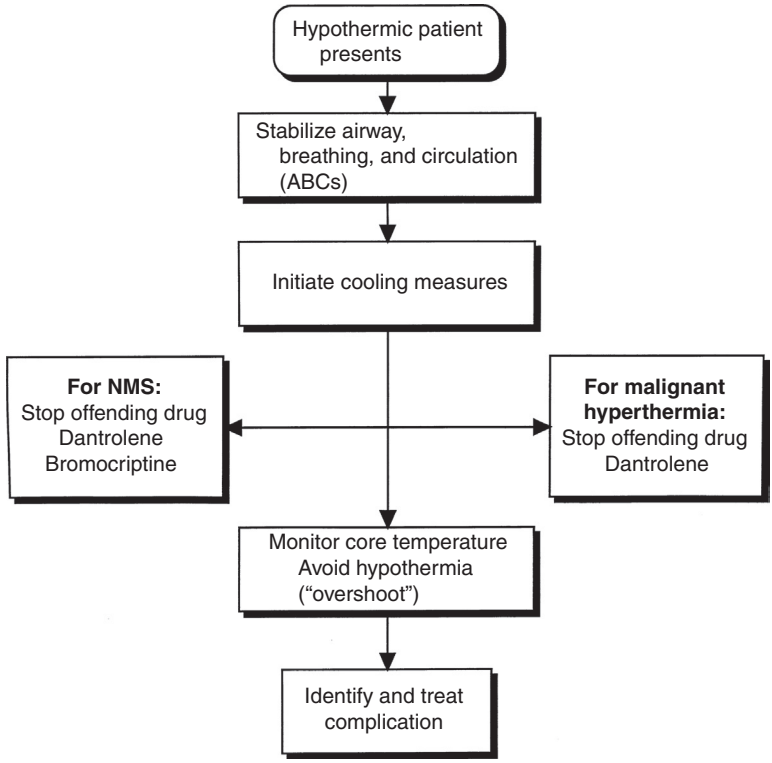


Figure 55.3 Schematic flow diagram outlining management of the hyperthermic patient. NMS, neuroleptic malignant syndrome.

For malignant hyperthermia, the mainstay of management is dantrolene administration, 2.5 mg/kg intravenously every 8 hours. After an initial response, it may be continued at a dose of 1.2 mg/kg orally four times a day for 3 days. Aggressive cooling measures and treatment of complications are initiated simultaneously.

Clinical Pearls and Pitfalls

1. Hypothermia and hyperthermia may be missed unless a true core temperature is obtained.
2. Initiation of therapy is often necessary before the cause is determined.
3. Early administration of parenteral antibiotics should be considered if occult sepsis is a possibility.
4. In severely hyperthermic patients, rapid cooling is best achieved by evaporation of lukewarm mist with fans. Cooling should be discontinued at a temperature of 39.5° C.
5. Heat stroke victims should not be assumed to be hypovolemic.
6. The role of ACLS medications in the management of hypothermic cardiac arrest is controversial.
7. Resuscitation of the hypothermic patient in cardiac arrest should be continued until the core temperature reaches at least 32° C.

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Casa DJ, McDermott BP, Lee EC, et al: Cold water immersion: the gold standard for exertional heatstroke treatment. Exerc Sport Sci Rev 35:141-149, 2007.

Rapid cooling improves the chances of survival of victims of exertional heatstroke. Cold water immersion is a simple, highly effective, and rapid cooling technique and has been used with great success in athletes. This article compares different cooling methods and details the advantages of cold water application.

Corneli HM: Accidental hypothermia. Pediatric Emergency Care 28(5):475-480, 2012.

This is a recent review covering the causes, evaluation, and management of hypothermia. Indications for external, core, and circulatory rewarming are discussed. The role for advanced life support interventions, medication administration, and defibrillation is described.

Laniewicz M, Lyn-Kew K, Silbergleit R: Rapid endovascular warming for profound hypothermia. Ann Emerg Med 51(2):160-163, 2008.

Rewarming of patients with severe hypothermia is often accomplished with cardiopulmonary bypass or pleural lavage, methods that are not always readily available. This case report describes the successful use of an endovascular temperature control catheter to rewarm a hemodynamically unstable woman who had become profoundly hypothermic following environmental exposure.

Lee CH, Van Gelder C, Burns K, et al: Advanced cardiac life support and defibrillation in severe hypothermic cardiac arrest. Prehosp Emerg Care 13:85-89, 2009.

The role of Advanced Cardiac Life Support (ACLS) interventions in hypothermic cardiac arrest is unclear. This case describes successful resuscitation of a hypothermic patient with rewarming, defibrillation, and ACLS medications. The contribution of each could not be determined, but the case suggests that ACLS care may be beneficial.

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The parkinsonism-hyperpyrexia syndrome is a rare, potentially fatal complication seen in Parkinson's disease. It results from suppression of central dopaminergic activity, most commonly developing following reduction of antiparkinson medications. It is clinically similar to neuroleptic malignant syndrome and is managed with dopaminergic drug replacement, supportive care, and treatment of complications.

Perry PJ, Wilborn CA: Serotonin syndrome vs neuroleptic malignant syndrome: a contrast of causes, diagnoses, and management. Annals of Clinical Psychiatry 24(2):155-162, 2012.

This is a recent review of serotonin syndrome and neuroleptic malignant syndrome. Both can present with altered mental status, autonomic nervous system dysfunction, and hyperthermia. The combination of elevated creatine kinase, liver function tests, and white blood cell count, with a low serum iron level, is more characteristic of neuroleptic malignant syndrome.

Seitz DP, Gill SS: Neuroleptic malignant syndrome complicating antipsychotic treatment of delirium or agitation in medical and surgical patients: case reports and a review of the literature. Psychosomatics 50:8-15, 2009.

Two case reports are presented followed by a review of the literature on neuroleptic malignant syndrome (NMS) resulting from antipsychotic treatment of delirium. Strategies to reduce the risk of NMS are discussed and include using low doses of medications, oral administration, and preferential use of atypical antipsychotics when possible.

Sultan N, Theakston KD, Butler R, et al: Treatment of severe accidental hypothermia with intermittent hemodialysis. CJEM 11:174-177, 2009.

This is a case report of the use of hemodialysis to rewarm a severely hypothermic man following environmental exposure. Advantages of hemodialysis over cardiopulmonary bypass in this context are discussed and include more widespread availability and the ability to correct electrolyte and acid-base disturbances.

van der Ploeg GJ: Goslings JC: Walpoth BH: Bierens JJ: Accidental hypothermia: rewarming treatments, complications and outcomes from one university medical centre. Resuscitation 81(11):1550-1555, 2010.

This is a retrospective cohort study of hypothermic patients. Etiologies included cold exposure or immersion in water, often in the context of intoxication, homelessness, or trauma. Fourteen rewarming techniques were used. Prognosis was worse in patients who were older, colder, or developed hypothermia indoors or from submersion.

CHAPTER 56

Smoke Inhalation and Carbon Monoxide Poisoning

Kevin C. Wilson ■ Arthur C. Theodore

Fires cause approximately 2500 deaths in the United States each year. Most are the result of smoke inhalation rather than burns. Smoke inhalation can cause death by several mechanisms, with carbon monoxide (CO) poisoning being the most common.

Fires are not the only cause of CO poisoning. Other potential causes include poorly functioning heating systems, improperly vented fuel-burning devices (e.g., furnaces, stoves, gasoline-powered electrical generators), and motor vehicles operating in poorly ventilated areas (e.g., parking garages). CO poisoning may also be intentional. Taken together, accidental and intentional CO poisoning causes 5000 to 6000 deaths in the United States each year.

Pathophysiology

Smoke inhalation may cause thermal injury, bronchopulmonary injury resulting from inhalation of toxins, oxygen depletion, or poisoning caused by CO, hydrogen cyanide, or other systemic toxins. Each is capable of inducing rapid systemic tissue hypoxia and death.

THERMAL AIRWAY INJURY

Thermal injury occurs when heat from the fire and smoke injures the mucosa of the airways, causing erythema, edema, and ulceration. The edema typically becomes noticeable within 24 hours, lasts 3 to 5 days, and may be severe enough to compromise airway patency.

The supraglottic airway is the most common site of thermal injury. Although rarely occurring, thermal injury to the lower airways tends to be severe and is often associated with the inhalation of steam.

TOXIN-MEDIATED LUNG INJURY

Smoke contains liquid droplets and elemental carbon that can adsorb toxic combustion products, such as acrolein, formaldehyde, phosgene, chlorine, perfluoroisobutylene, sulfur dioxide, nitrogen dioxide, and nitric oxide (Table 56.1). Inhalation of such toxins can directly injure the respiratory mucosa of the upper and lower airways, as well as the alveolar spaces. This can occur even in the absence of thermal injury.

Chemical injury to the airways causes focal corrosion, neutrophilic airway inflammation, and disruption of mucociliary transport. Damage to the mucosal barrier can lead to increased susceptibility to respiratory infections. Alveolar injury occasionally results in the acute respiratory distress syndrome (ARDS), with increased alveolar and capillary permeability, interstitial and alveolar edema, impaired lymphatic flow, neutrophilic inflammation, hyaline membrane formation, and worsened ventilation-perfusion mismatching (see Chapter 73). Individuals who survive may develop fibrosis.

TABLE 56.1 ■ **Toxic Products of Combustion**

Chemical	Sources	Injury Produced
Aldehydes	Plastic from furniture	Upper airway injury and CNS depression
Acrolein	Acrylics from windows, wood finishes, or wall coverings	Diffuse airway and alveolar injury
Ammonia	Phenolics and nylon	Upper airway injury
Anhydrides	Chemical, paint, plastics	Airway injury, asthma, pulmonary hemorrhage with high-dose exposure
Carbon dioxide	Closed space fires (as high as 10% CO_2)	Respiratory acidosis, CNS depression
Cyanide	Carpets, upholstery, nylon, polyurethane products from isocyanates	Acidosis, shock, asthma, airway injury, hypersensitivity pneumonitis
Hydrogen chloride	Fabrics, polyvinyl chloride	Mucosal burns and edema, dysrhythmias, shock
Hydrogen fluoride	Polytetrafluoroethylene (Teflon) from pipes or kitchen utensils	Upper airway injury
Nitrogen dioxide	Nitrocellulose	Alveolar injury

CNS, central nervous system; CO_2 carbon dioxide.
Modified from Sheppard D: Noxious gases: pathogenetic mechanism. In Baum G, Wolinsky E (eds): Textbook of Pulmonary Diseases, 4th ed. Boston: Little, Brown, 1989, pp 840-841.

The extent and location of the injury depend on the duration of exposure, the patient's minute ventilation, particle size, and water solubility of the toxins. A long duration of exposure or a high minute ventilation favors more severe bronchopulmonary injury. Small particles (<0.1 micron in diameter) are deposited primarily in the lung parenchyma, whereas larger particles (2 to 5 microns) are distributed throughout the respiratory tract.

OXYGEN DEPLETION

During a fire, the air becomes hypoxic because the fire consumes ambient oxygen. Breathing hypoxic air decreases the alveolar oxygen concentration, which decreases the amount of oxygen available to bind hemoglobin or dissolve in the blood. The consequence is less oxygen delivery to the tissues and systemic tissue hypoxia.

Systemic Toxins

A variety of systemic toxins are inhaled during a fire, many of which can induce systemic tissue hypoxia via a variety of mechanisms. Examples include CO and hydrogen cyanide poisoning. CO forms carboxyhemoglobin (COHb) and impairs the delivery of oxygen to the tissues, whereas hydrogen cyanide binds to the mitochondrial cytochrome complex and interferes with the utilization of oxygen by the tissues. The effects of systemic toxins are frequently synergistic.

Carbon Monoxide

CO is a colorless, odorless, tasteless, nonirritant gas that is normally present at ambient concentrations of less than 0.001%. CO uptake into the lung is augmented when there is an increase in the ambient concentration of CO, the duration of exposure to CO, or the minute ventilation. In these situations, CO rapidly diffuses from the alveolus into the blood and binds hemoglobin, forming COHb. This competitively inhibits the formation of oxyhemoglobin, because CO binds

to hemoglobin with an affinity that is 230 times greater than the affinity of oxygen for hemoglobin. The result is diminished oxygen delivery to the tissues and systemic tissue hypoxia.

Decreased oxyhemoglobin formation is not the only mechanism by which CO impairs oxygen delivery. Both CO poisoning and the respiratory alkalosis that commonly accompanies it shift the oxyhemoglobin dissociation curve to the left, which impairs the release of the oxygen to the tissues (see Figure A.1B in Appendix A). The shift of the oxyhemoglobin dissociation curve to the left is a consequence of a CO-induced conformational change of the hemoglobin, making it more oxygen avid.

Fetuses are particularly susceptible to the detrimental effects of CO poisoning because CO has significantly greater affinity for fetal hemoglobin than hemoglobin A. As a consequence, fetal demise often occurs in pregnant women who are otherwise successfully treated for CO poisoning.

Approximately 10% to 15% of the CO that diffuses from the alveolus binds to extravascular proteins (e.g., myoglobin, cytochrome-c oxidase, guanylate cyclase, nitric oxide synthase) instead of hemoglobin. This CO slowly dissociates from the extravascular proteins, creating a delayed phase of CO toxicity characterized by persistent derangements of oxidative metabolism, as well as myocardial and skeletal muscle function. Neurologic sequelae are due to perivascular neural injury caused by oxidative injury from oxygen-free radicals.

By the time the delayed phase occurs, COHb levels are often normal because the CO has dissociated from hemoglobin. The half-life of COHb is approximately 320 minutes when a patient is breathing ambient air with 21% oxygen concentration at sea level. This half-life is reduced to 60 minutes if the patient breathes 100% oxygen, and it is further reduced to 23 minutes if the patient breathes 100% oxygen under 2.5 to 3 atmospheres of pressure. The latter is referred to as hyperbaric oxygen (HBO). In addition to reducing the half-life of COHb, HBO can increase the amount of oxygen dissolved in plasma to a level sufficient to meet the basal oxygen requirements of tissues, even in the absence of functional hemoglobin.

Acceleration of CO excretion and augmentation of oxygen delivery are the primary rationales for HBO therapy in acute CO poisoning, which is discussed later. However, HBO therapy may also prevent the formation of oxygen species responsible for brain lipid peroxidation and thereby limit the extent and frequency of delayed neurologic sequelae.

Hydrogen Cyanide

Cyanide avidly binds to the ferric ion of cytochrome-c oxidase a3 (the final enzyme in the mitochondrial cytochrome complex) and other enzymes of the Krebs cycle, halting electron transport and the process by which hydrogen ions are converted to adenosine triphosphate (ATP). This cessation of aerobic metabolism forces the cell to convert to anaerobic metabolism in order to generate the ATP that is necessary for survival. The inability to utilize oxygen, even if amply supplied to tissues, is particularly deleterious to the cardiovascular and central nervous systems.

Cyanide poisoning may exacerbate central nervous system injury by numerous other mechanisms. First, inhibition of antioxidants (e.g., catalase, glutathione reductase, superoxide dismutase) leads to the accumulation of toxic oxygen-free radicals. Second, release of glutamate causes detrimental stimulation of *N*-methyl-D-aspartate (NMDA) receptors. Finally, inhibition of glutamic acid decarboxylase reduces the seizure threshold.

Clinical Manifestations

Most of the clinical findings of acute smoke inhalation are apparent early, although delayed manifestations are known to occur. Chronic smoke inhalation typically presents differently than acute smoke inhalation.

EARLY CLINICAL FINDINGS

The symptoms and signs of acute smoke inhalation reflect the presence of airway injury, systemic tissue hypoxia, or both. Upper airway injury typically manifests as hoarseness or stridor, accompanied by cervical burns, oropharyngeal burns, or singed facial hair. In contrast, lower airway injury is more likely to induce carbonaceous sputum, crackles, rhonchi, or wheezes. These findings may not develop until more than 24 hours after smoke inhalation.

Systemic tissue hypoxia may cause obtundation or restlessness, lactic acidosis, rhabdomyolysis, or end organ damage. The types of end organ damage that are frequently seen include acute kidney injury (e.g., acute tubular necrosis), myocardial ischemia, and hepatic failure. Patients with systemic tissue hypoxia usually have a high minute ventilation from both tachypnea and large tidal breaths, probably reflecting respiratory compensation for the metabolic acidosis. With severe obtundation, such compensation may not be possible, resulting in hypoventilation and hypercapnic respiratory failure.

In addition to the manifestations of systemic tissue hypoxia just described, there may be findings related to the toxin(s) that precipitated the systemic tissue hypoxia (Table 56.2). Slight elevation of the CO level may be asymptomatic in healthy individuals or cause exacerbations of preexisting cardiopulmonary disease (e.g., coronary artery disease, chronic obstructive pulmonary disease). Mild CO poisoning (usually less than 25% COHb) is characterized by headache, dyspnea, nausea, lethargy, and neuromotor abnormalities. Patients with moderate CO poisoning (typically 25% to 40% COHb) may have vomiting, mild weakness, and syncope. Myocardial ischemia and ventricular arrhythmias may also occur. Severe CO poisoning (usually greater than 40% COHb) is associated with loss of consciousness, seizures, and severe weakness. Coma may be associated with severe cerebral edema and is often a prelethal state. The bluish coloration of cyanosis does not occur, because COHb has a cherry red color. The skin may appear pink and the lips red.

Exposure to hydrogen cyanide often first results in eye irritation. Inhalation of even small amounts of hydrogen cyanide may induce headache, anxiety, nausea, and a metallic taste. The characteristic bitter almond odor of cyanide can be detected at levels of 2 to 10 ppm. The ability to detect the odor of cyanide is a genetic trait present in 60% to 80% of people and not a reliable indicator of heavy exposure.

DELAYED CLINICAL FINDINGS

Several components of smoke have been linked to the development of the reactive airways dysfunctional syndrome (RADS), an asthma-like condition of bronchial hyperresponsiveness that follows an inhalational injury. RADS is characterized by cough, sputum production, and wheezing. Affected individuals generally seek medical attention within 24 hours of exposure. The condition tends to be persistent for at least 3 months, but it may persist for years or become permanent.

TABLE 56.2 ■ **Carboxyhemoglobin Concentration and Clinical Effects**

Carboxyhemoglobin Percentage Concentration	Severity	Expected Symptoms
< 25%	Mild	Psychomotor impairment, headache, dyspnea, nausea, lethargy, mild weakness
25%–40%	Moderate	Vomiting, syncope, severe weakness
> 40%	Severe	Loss of consciousness, seizures, dysrhythmias
60%	Potentially lethal	Coma
70%	Lethal	Death

As many as 40% of patients with acute CO poisoning develop delayed neurologic sequelae if not adequately treated. These sequelae typically occur 3 to 40 days after apparent recovery from the acute episode. Findings include variable degrees of aphasia, apraxia, apathy, disorientation, hallucinations, bradykinesia, cogwheel rigidity, gait disturbances, incontinence, personality changes, and mood changes. These abnormalities may become permanent. Neuroimaging studies (e.g., computed tomography, magnetic resonance imaging) may reveal abnormalities that are characteristic of CO toxicity, including bilateral necrosis of the globus pallidus, cerebral cortex, hippocampus, and substantia nigra.

Hydrogen cyanide inhalation may also cause various delayed neurologic sequelae, with parkinsonism the most common.

CHRONIC TOXICITY

Although smoke inhalation causes acute CO or hydrogen cyanide poisoning, other sources may cause chronic toxicity. Patients with chronic CO intoxication tend to have nonspecific, low-grade symptoms, such as malaise and fatigue. This makes accurate diagnosis notoriously difficult. More than one third of cases are never diagnosed. Patients with chronic hydrogen cyanide intoxication also tend to have vague symptoms. These include headache, abnormal taste, abdominal pain, and anxiety.

Management

Smoke inhalation is an acute, life-threatening condition. As a result, there is seldom time to confirm the diagnosis prior to initiating treatment. The diagnostic evaluation and therapeutic interventions must occur concomitantly.

INITIAL EVALUATION

When someone is rescued from a fire, the initial patient evaluation and management should follow the algorithms of Advanced Trauma Life Support (ATLS; see Chapter 95). The presence of symptoms or signs that suggest the airway may be compromised should prompt intubation (emergent tracheostomy is occasionally necessary [Chapter 30]). Examples include stridor, hoarseness, full-thickness burns of the face or neck, mucous membrane burns, severe central nervous system depression, or laryngoscopic evidence of laryngeal edema. Regardless of whether intubation occurs, administer 100% oxygen.

All patients should have a COHb level measured by co-oximetry to assess for CO poisoning, because standard pulse oximetry cannot differentiate COHb from oxyhemoglobin. The level of COHb measured by co-oximetry that is considered abnormal depends on whether the patient is a smoker. A COHb level > 3% is abnormal in nonsmokers, whereas a COHb level > 10% is abnormal in current smokers. The arterial oxygen tension and oxyhemoglobin saturation may be normal, even when severe CO poisoning exists.

In addition to a COHb level, initial laboratory studies should include a complete blood count, serum chemistry panel, toxicology screen, lactate level, creatine kinase level, troponin level, and lactate dehydrogenase level. Elevated lactate, creatine kinase, troponin, or lactate dehydrogenase levels suggest hypoxia-induced systemic tissue damage. Cyanide levels generally need not be measured because the decision whether to treat hydrogen cyanide poisoning must be made before the results are available.

An electrocardiogram (ECG) should also be obtained. ECG abnormalities (e.g., ST segment and T wave changes) indicate hypoxia-induced myocardial ischemia. Chest radiographs are frequently unremarkable despite significant hypoxemia. Generalized haziness suggests interstitial edema or early ARDS.

CARBON MONOXIDE POISONING

Asymptomatic patients with a COHb level less than 10% and no neurologic or hemodynamic instability do not require therapy for CO poisoning. All other patients should receive 100% oxygen delivered by tight-fitting mask or by endotracheal intubation. Cardiac monitoring is essential for all patients with CO poisoning, as ventricular arrhythmias cause most early deaths. The primary clinical decision that needs to be made is whether supplemental oxygen alone is sufficient or whether HBO therapy is indicated.

HBO therapy is controversial because of a paucity of high-quality or consistent evidence. However, the following approach is reasonable given the current body of evidence (Figure 56.1).

Patients with mild CO poisoning (described earlier; see Table 56.2) can be treated with supplemental oxygen alone (using a 100% non-rebreather mask) until the COHb level is less than 5% and signs of cardiovascular, neurologic, or other toxicities have resolved.

Patients with moderate CO poisoning (described earlier; see Table 56.2) are selected for HBO therapy on an individualized basis. The evidence indicates that HBO therapy probably does not

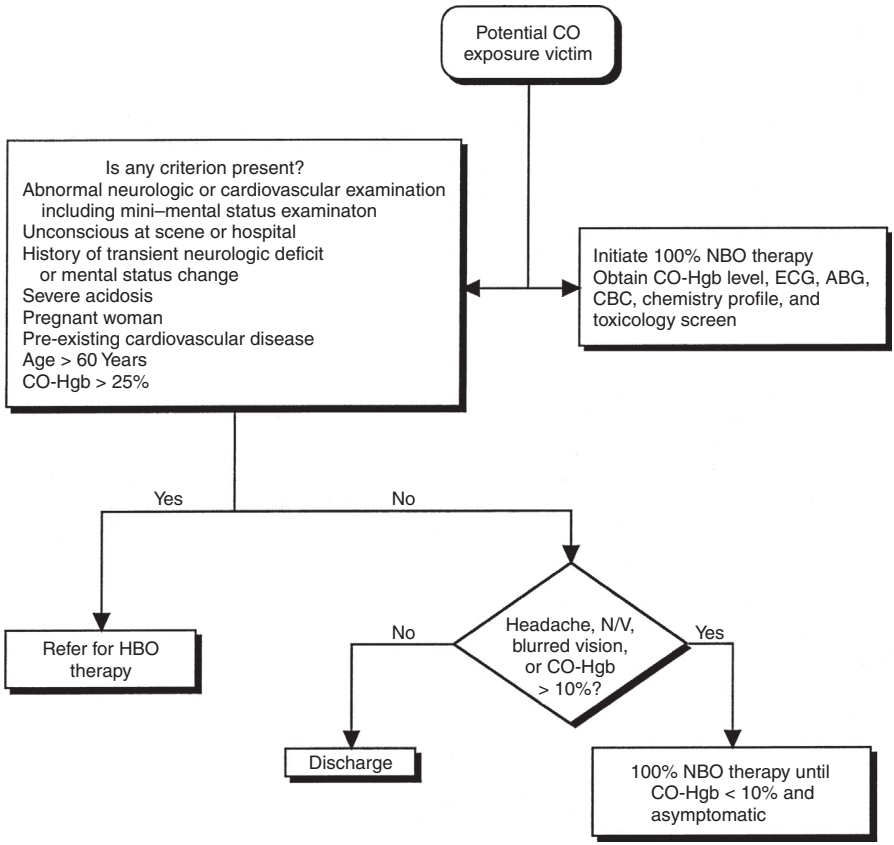


Figure 56.1 Schematic flow diagram to treat carbon monoxide (CO) poisoning. ABG, arterial blood gas; ECG, electrocardiogram; CBC, complete blood count; CO-Hgb, carboxyhemoglobin; HBO, hyperbaric oxygen; NBO, normobaric oxygen; N/V, nausea and vomiting. *(Modified from Thom SR: Smoke inhalation. Emerg Med Clin North Am 7:371-387, 1989.)*

improve mortality in these patients, but it may reduce the incidence of delayed neurologic sequelae when instituted early (two treatments initiated within 6 hours of exposure). Some centers limit HBO therapy to those moderate CO poisoning patients with an increased risk for morbidity or mortality (Box 56.1).

Patients with severe CO poisoning (see Table 56.2) should be considered for early referral to the nearest facility that offers HBO therapy. In these patients, HBO appears to hasten the resolution of symptoms and reduce the risk of delayed, permanent neurologic sequelae.

HYDROGEN CYANIDE POISONING

Treatment for hydrogen cyanide poisoning should be considered for patients with severe CO poisoning, persistent acidosis, or a reduced arteriovenous difference in oxygen content. One should consider cyanide treatment for patients exposed to fires involving carpets, upholstery, nylon, or polyurethane products from isocyanates (see Table 56.1). Treatment consists of amyl nitrite, sodium nitrite, and sodium thiosulfate.

Amyl nitrite perles are generally administered first. A perle is broken onto a gauze pad and then held under the nose, over the Ambu-valve intake, or under the lip of the face mask. The patient inhales for 30 seconds every minute. A new perle should be used every 3 minutes until a sodium nitrite infusion is ready.

Sodium nitrite should be infused intravenously as soon as possible, unless the patient has responded to the amyl nitrite. The usual adult dose of sodium nitrite is 10 mL of a 3% solution (300 mg) infused for 5 minutes or longer. The usual pediatric dose is 0.12 to 0.33 mL/kg body weight up to 10 mL, also infused as a 3% solution for 5 minutes or longer. The blood pressure should be monitored closely during sodium nitrite administration, and if hypotension develops, the infusion should be slowed.

Patients without a satisfactory response to amyl nitrite or sodium nitrite should receive an infusion of intravenous sodium thiosulfate next. The usual adult dose is 50 mL of a 25% solution (12.5 g) infused for 10 to 20 minutes. The usual pediatric dose is 1.65 mL/kg of a 25% solution. The sodium nitrite and sodium thiosulfate can be again administered at half of the initial dose 30 minutes later if there is an inadequate clinical response. However, the methemoglobin level should be measured prior to selecting the agent. If the methemoglobin level approaches 20%, sodium thiosulfate should be preferentially administered because amyl nitrite and sodium nitrite oxidize the ferrous iron of hemoglobin to methemoglobin.

BOX 56.1 ■ Relative Indications for Hyperbaric Oxygen Therapy for Patients According to Severity Carbon Monoxide (CO) Poisoning*

Mild CO poisoning: None
Moderate CO poisoning: Patients with the following:
- Preexisting cardiovascular disease
- Age > 60 years
- Pregnancy
- Prolonged CO exposure
- History of loss of consciousness during or immediately after exposure
- Ongoing end-organ ischemia (e.g., severe metabolic acidosis [pH < 7.1], myocardial ischemia)
- Neurologic deficits or mental status changes.

Severe CO poisoning: All patients

**Severity as defined in Table 56.2.*

ONGOING MANAGEMENT

Other than the interventions that target CO and hydrogen cyanide poisoning, most therapies for smoke inhalation are supportive. Humidification of supplemental oxygen may alleviate mucous membrane dryness and discomfort while minimizing inspissation of secretions. Inhaled beta agonists may relieve bronchospasm caused by airway injury, but avoid anticholinergic agents because of their potential drying effects. Corticosteroids have been used in patients with refractory bronchospasm; however, they should not be used routinely to treat airway edema because they have been associated with increased mortality. Despite the high incidence of infection associated with surface burn and inhalation injuries, prophylactic antibiotics are not indicated because they may promote the emergence of resistant organisms.

All patients should have an airway examination via fiberoptic bronchoscopy. The purpose of fiberoptic bronchoscopy is to examine the subglottic airway for airway injury. Early findings in patients with thermal or toxin-mediated airway injury include mucosal edema, erythema, blistering, hemorrhage, ulceration, soot deposition, and airway narrowing. Later findings include crusts, mucous plugs, and bronchial casts formed from sloughed epithelium. Because airway injury is likely to increase over the first 24 hours and persist for 3 to 5 days, the information may help the clinician decide whether intubation or tracheostomy is indicated or when an intubated patient can be safely extubated.

Serial measurements of lactate, creatine kinase, and lactate dehydrogenase may be helpful for assessing whether the hypoxic injury is improving, stable, or worsening. Serial electrocardiograms are similarly recommended if an initial electrocardiogram was abnormal (e.g., ST interval changes), in order to follow the course of hypoxia-induced myocardial injury.

Outcomes

Fires cause approximately 2500 deaths in the United States each year. Most are the result of smoke inhalation. For the individual patient, the outcome depends on the severity of the exposure and the preexisting health of the patient. For those whose smoke inhalation is complicated by acute CO poisoning, the overall mortality has been estimated to be as high as 31%. Significant morbidity persists in up to 40% of patients.

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CHAPTER 57

Drug Overdoses and Toxic Ingestions

Pia Chatterjee ■ Jeanmarie Perrone

Successful management of patients after a life-threatening drug overdose depends on emergency medical system (EMS) and emergency department (ED) personnel (1) initiating the critical interventions of airway management and cardiovascular stabilization, (2) simultaneously obtaining a thorough history, and (3) targeting specific therapies based on the suspected exposure. Communication between the ED and the intensive care unit (ICU) will be paramount for continuing successful resuscitations in the ICU.

Not all "drug overdoses" are intentional. Toxic ingestions may be accidental or result from the ingestion of products stored inappropriately—for example, lye stored in a soda bottle. Iatrogenic dosing errors and excess self-medication of drugs with narrow therapeutic:toxic ratios (salicylates, lithium, digoxin) also occur. Occasionally, chronic medications precipitate acute toxicity caused by a drug interaction or a change in drug metabolism. Acute management of poisoned patients will depend on the ingestion; however, disposition of patients following ICU care depends on whether or not the overdose was intentional.

Although deep sedation and coma in patients admitted to the ICU may be attributed to a drug ingestion, patients with unclear histories should undergo evaluation for other causes of altered mental status. Intracranial pathologic conditions should be excluded by computed tomographic (CT) scan of the head, and lumbar puncture should be considered in febrile patients.

The regional poison center is an additional important resource in the management of any suspected poisoning, including those resulting from "new" recreational drugs with serious toxic side effects, such as "bath salts" or synthetic cannabinoids ("K2/Spice"), and new therapies including use of lipid therapy for hemodynamically significant poisonings.

Mechanisms of Injury

DIRECT DRUG EFFECTS

Nearly all drugs produce harmful effects if taken in excessive amounts. Systemic toxicity is due to selective effects of the toxin or a metabolite on specific targets, such as binding to specific receptors (therapeutic drugs), disruption of metabolic pathways (cyanide, salicylates, iron), cellular production of toxic metabolites (acetaminophen in the liver, methanol in the retina, ethylene glycol in the kidney), and enzymatic inhibition (Na^+/K^+-ATPase by digoxin; anticholinesterase by organophosphates). Some toxins produce effects by several mechanisms. For example, isoniazid causes both hepatotoxicity via a cytochrome P-450 pathway metabolite and neurotoxicity via the inhibition of pyridoxal 5′-phosphate. Pathologic effects may also occur at the site of exposure as a result of cytotoxic chemical reactions (e.g., caustic acid or alkali ingestions) that damage exposed tissue.

COMPLICATIONS

Aspiration occurs in poisoned patients as a complication of vomiting, orogastric lavage, endotracheal intubation, or loss of airway reflexes because of obtundation. Early assessment and definitive airway management are critical in diminishing the risk of aspiration. Acute lung injury may complicate recovery following life-threatening ingestions. Hyperthermia may occur for several reasons: increased motor activity that occurs with agitation or seizures, direct drug effects on the hypothalamus (sympathomimetics), or aspiration and pneumonia. Rhabdomyolysis (see Chapter 81) can occur in patients after prolonged periods of immobilization because of obtundation, protracted agitation or seizures, or cocaine or amphetamine use. Under these circumstances, aggressive hydration and maintenance of urine output are important. Acute renal failure (see Chapter 81) may occur directly, for example, from ethylene glycol direct toxic effects on the kidneys or secondarily, for example, from drug-induced hypotension. Acute hepatic failure (see Chapter 59) most commonly results from acetaminophen poisoning but may also occur because of the multiorgan effects of diffuse toxins such as mercury or iron.

Management

DIAGNOSTIC APPROACH

Initial assessment of the airway, breathing, and circulatory status (ABCs) and frequent reassessment are critical to monitoring the dynamic status of ongoing toxicity. Empty pill bottles or discussions with family members regarding medicines available in the home are helpful in focusing the diagnostic workup. Physical examination should screen for manifestations of common toxic syndromes ("toxidromes")—for example, anticholinergic, opioid, or salicylate toxicity. An electrocardiogram can screen for conduction defects associated with cyclic antidepressants, calcium channel antagonists, beta-blockers, or digoxin. QR and QT prolongation herald impending cardiotoxicity and should be followed serially. Toxicology screening should be performed if the results will be available in a sufficiently short time frame to be clinically relevant. All patients with intentional ingestions should have an acetaminophen level checked to exclude a clinically silent, potentially overlooked but treatable acetaminophen ingestion.

THERAPEUTIC APPROACH

After initial stabilization of the ABCs, certain therapies should be considered in all poisoned patients. Suspected hypoglycemia should be treated with an intravenous (IV) bolus of concentrated dextrose solution (50 mL of 50% dextrose). Patients with the triad of signs suggesting opioid toxicity (respiratory depression, pinpoint pupils, and coma) warrant treatment with the opioid antagonist naloxone. IV fluid therapy is important in many patients with overdoses to compensate for volume losses associated with vomiting. Parenteral benzodiazepine sedation is indicated for agitated or uncooperative patients because it may prevent rhabdomyolysis, hyperthermia, and injuries to the patient or staff as well as decrease the risk of seizures.

Gastrointestinal (GI) decontamination is no longer routinely recommended for most overdose patients but may have a limited role in some patients with serious toxicity admitted to the ICU. Orogastric lavage via a large-bore tube (Ewald tube) may be critical in patients ingesting large quantities of drugs not bound by activated charcoal, such as iron or lithium. It can be life saving in serious calcium channel antagonist overdoses by removing a clinically significant fraction of drug, decreasing toxicity. Orogastric lavage should only be considered in patients manifesting signs of toxicity following a potentially life-threatening ingestion, and only perform it after the judging the patient's airway to be protected, often necessitating endotracheal intubation.

TABLE 57.1 ■ **Antidotes and Adjuncts in the Therapy of Selected Poisonings**

Toxin	Antidote	Dosing for Adults and Comments
Acetaminophen	*N*-acetylcysteine	Orally 140 mg/kg × 1; followed by 70 mg/kg every 4 hours × 17 doses
		IV: 150 mg/kg IV over 60 minutes, followed by an infusion of 12.5 mg/kg/h over a 4-hour period, and finally an infusion of 6.25 mg/kg/h over a 16-hour period
Anticholinergic agents	Physostigmine	1–2 mg IV over 5 minutes; use with caution for severe delirium (may cause seizures, bronchospasm, asystole, cholinergic crisis)
Beta-adrenergic antagonists	Glucagon	2–5 mg IV; titrate repeat doses; may use infusion of 2–10 mg/h
Calcium channel blockers	Calcium gluconate	1 g (10 mL of 10% solution) IV over 5 minutes with electrocardiographic monitoring; repeat as needed, check serum calcium after third dose
	Insulin	Bolus dose of 0.1 U/kg followed by an infusion of 0.5 mg/kg/h; can be titrated up to a rate of 1 U/kg/h with a dextrose infusion to maintain euglycemia
Cyclic antidepressants	Sodium bicarbonate	1–2 mEq/kg IV; titrate to arterial pH of 7.5 or electrocardiographic alterations (see text)
Digoxin	Digoxin antibodies (Digibind)	Vials (number) = (digoxin level [ng/mL] × weight [kg])/100 or
		10–20 vials for a life-threatening arrhythmia
Methanol Ethylene glycol	Fomepizole	Loading dose of 15 mg/kg IV over 30 minutes; subsequent 4 doses every 12 hours at 10 mg/kg; further dosing per poison center
Opioids	Naloxone	0.05–0.4 mg IV, repeat as needed; infusion: two thirds of reversal dose/h, titrate to effect

Oral activated charcoal can diminish the absorption of many drugs and can enhance drug excretion for some agents via GI dialysis (the diffusion of high plasma drug levels back into the gut lumen to be bound to activated charcoal and excreted) or interruption of enterohepatic circulation of active metabolites. Sustained release preparations (e.g., calcium channel blockers) and drugs not bound to activated charcoal (e.g., lithium, iron) may be cleared from the gut using whole bowel irrigation. Bowel irrigation is performed with polyethylene glycol–electrolyte lavage solutions (e.g., GoLYTELY, CoLYTE) administered via nasogastric tube at a rate of 1 to 2 L/h in adults.

The regional poison control center should be consulted to obtain general management and toxin-specific therapeutic advice, as many common toxins have specific therapies or antidotes (Table 57.1).

Common Toxic Ingestions

ACETAMINOPHEN

Acetaminophen is one of the most commonly ingested medications. Few patients become seriously ill from acetaminophen overdose because of early diagnosis and antidote treatment with *N*-acetylcysteine (NAC). Life-threatening hepatotoxicity, however, occurs in the few who present late after their ingestions or in whom clinicians fail to recognize acetaminophen when it is co-ingested with other drugs.

Patients with a history of acetaminophen ingestion should have a > 4-hour post ingestion acetaminophen level obtained and interpreted using the Rumack-Matthew nomogram (Figure 57.1). Nausea, vomiting, and sometimes right upper quadrant abdominal pain are associated with toxic hepatitis from ingestions a day or two earlier. Patients with jaundice or coagulopathy or those reporting a large acetaminophen ingestion 1 to 3 days previously should be presumed to have hepatotoxicity and should have treatment initiated immediately. When presentations are delayed more than 24 hours after ingestion, acetaminophen levels may be low or zero, but significant elevations in transaminases and prothrombin time reflect severe acetaminophen poisoning.

Therapeutic doses of acetaminophen are metabolized in the liver by glucuronidation (60%), sulfation (30%), or by the P-450 cytochrome oxidase system (4%). The last pathway results in a toxic intermediate, N-acetyl-p-benzoquinoneamine (NAPQI). NAPQI is then normally reduced by glutathione, which prevents toxicity. With increasing dose or overdose, more acetaminophen metabolism is shunted into the P-450 system, depleting glutathione. As a result, NAPQI accumulates and induces centrilobular necrosis of the liver. The antidote NAC replenishes the glutathione and prevents hepatic necrosis (Chapter 59).

Patients with toxic acetaminophen levels require a loading dose of NAC (140 mg/kg) and subsequent dosing every 4 hours (70 mg/kg) for an additional 17 doses over 72 hours. NAC can also be given parenterally with a loading dose of 150 mg/kg IV over 60 minutes then by continuous

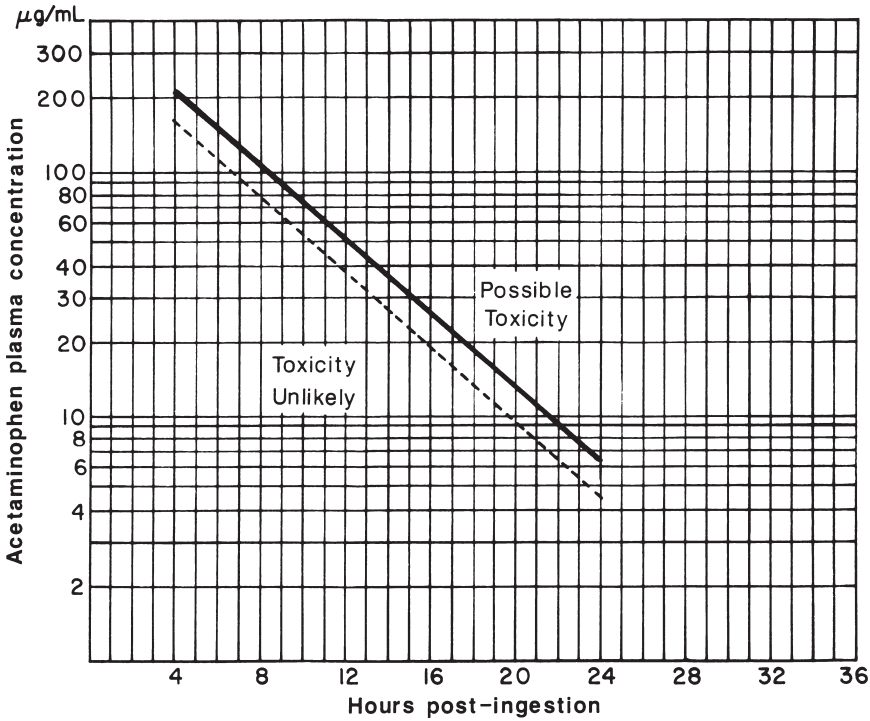


Figure 57.1 The Rumack-Matthew nomogram *(solid line)* estimates the likelihood of hepatotoxicity in acute acetaminophen overdose. *N*-acetylcysteine (NAC) therapy is recommended if the acetaminophen plasma level at 4 hours (or later) after ingestion plots above the broken line. For example, patients with levels greater than or equal to approximately 150 μg/mL at 4 hours or greater than or equal to approximately 35 μg/mL at 12 hours after ingestion should be treated with NAC (see text). The broken line allows a 25% variability below the solid line to take into account inaccuracies in estimated time of ingestion or measurement of plasma level. *(Adapted from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity. Pediatrics 44:871-876, 1975.)*

IV infusion over 20 hours (see Table 57.1). Although most effective within the first 8 hours after overdose, NAC therapy is effective up to 24 hours after overdose as well as in patients with fulminant hepatic failure secondary to acetaminophen. The current recommended dose and route of administration (orally versus IV) in these situations can be obtained via the local poison center. NAC should be continued until the acetaminophen level is zero and the liver function tests are trending down.

ALCOHOLS

The clinical effects of *ethanol* intoxication can range from giddiness to coma and is affected by time and quantity ingested, tolerance, and co-ingestants. When presented with patients with presumed ethanol-induced altered mental status, although debated in the literature, measurement of ethanol levels may confirm the clinical correlation as well as prevent inappropriate assumptions that high ethanol levels are the etiology of the altered mental status in any one patient. The initial evaluation of any patient acutely intoxicated with alcohol should address whether significant co-ingestants may be present and add to impending morbidity. Such considerations include ingestion of other central nervous system (CNS) depressants that may add to eventual respiratory depression such as benzodiazepines or other sedatives, as well as the ingestion of toxic alcohols as ethanol substitutes.

The toxic alcohols to consider include methanol, ethylene glycol, and isopropanol. Methanol is found in Sterno, windshield washer fluids, and industrial solvents. Ethylene glycol is the principal ingredient in most antifreeze preparations and is also used in deicing agents. Isopropanol is commonly used as rubbing alcohol and as a solvent in home products. These substances are readily available to ingest as an alcohol substitute in patients who are made abstinent from alcohol or, in other cases, secondary to suicidal intention. The presence of an anion gap acidosis in a patient with suspected ethanol intoxication should promote a diagnostic search for the presence of methanol or ethylene glycol. The findings of an osmolar gap or anion gap acidosis can be helpful when making the diagnosis but must be interpreted with caution depending on the time since ingestion and the amount of metabolism that may have occurred. Soon after ingestion, either ethanol or a toxic alcohol will cause an elevated osmolar gap because all alcohols are osmotically active. Over several hours, this osmolar gap will diminish, whereas an anion gap acidosis will develop if methanol or ethylene glycol were ingested instead of ethanol. These toxic alcohols will undergo metabolism to an organic acid (formic acid in methanol poisoning and glycolic acid and oxalic acid in ethylene glycol poisoning). This acidosis, as well as the exclusion of other causes of metabolic acidosis (lactic acid, salicylate ingestion), helps confirm the suspicion of toxic alcohol ingestion while confirmatory methanol and ethylene glycol levels are obtained.

Other clinical symptoms that suggest toxic alcohol ingestion are alcohol specific. Methanol exposure is characterized by visual symptoms that develop within 12 to 24 hours of exposure. Patients complain of "snow field" vision that occurs from formic acid–mediated retinal toxicity. Ethylene glycol may cause acute tubular necrosis and acute renal failure 12 to 48 hours after ingestion because of calcium oxalate precipitants in the kidneys. The principal toxicity of isopropanol ingestion is CNS depression, lethargy, and coma as well as ketosis but not a metabolic acidosis because isopropanol is metabolized to acetone contributing to an osmolar gap but not an anion gap acidosis.

Laboratory testing should include finger-stick glucose, electrolytes, ethanol level with other alcohols, and serum osmolarity. Urine fluorescence with a Wood's lamp can detect the presence of antifreeze (and presumably ethylene glycol) shortly after ingestion; however, this finding is not always present. An electrocardiogram (EKG) may show QT prolongation secondary to hypocalcemia from calcium oxalate precipitation in the kidneys.

Fomepizole, like ethanol, blocks metabolism of the toxic alcohols by competitively inhibiting the enzyme alcohol dehydrogenase and is the recommended treatment for suspected ethylene glycol and methanol poisoning. When available, fomepizole is preferred to an ethanol infusion because it does not require following serum ethanol levels and increases safety by not adding synergistic respiratory depression. Hemodialysis still has a role in toxic alcohol ingestions and should be discussed with the nephrology team. Traditional indications for hemodialysis include severe acidosis, renal failure, or inability to obtain fomepizole or ethanol therapy. If an elevated level of ethylene glycol or methanol is discovered, administer fomepizole, but if an acidosis is not yet present, some patients can be managed expectantly with fomepizole and not dialysis.

CALCIUM CHANNEL AND BETA-ADRENERGIC ANTAGONISTS

Accidental or intentional ingestion of the potent calcium channel blockers or beta-adrenergic antagonists can result in significant morbidity and fatalities. Patients present with bradycardia and hypotension. The mental status may be normal or reflect obtundation, seizures, or coma following beta-blocker poisoning, and it typically remains normal despite significant hypotension in the setting of calcium channel blocker poisoning. Poisoning with these drugs must be considered in any young person with unexplained bradycardia and may be misdiagnosed as a complicated myocardial infarction or conduction defect in older patients. Sustained release preparations may produce delayed onset of toxicity and profound decompensation may occur after a period of relative stability.

Because beta-adrenergic antagonists decrease intracellular cyclic adenosine monophosphate, a specific therapeutic role has been demonstrated for the hormone glucagon. Glucagon increases myocardial cyclic adenosine monophosphate via a non–beta-adrenergic receptor mediated mechanism. Following a trial of atropine, glucagon should be given (3 to 10 mg IV bolus followed by a 2 to 5 mg/h IV infusion).

Calcium channel antagonists block slow inward calcium channels on vascular smooth muscle and myocardial cells, causing conduction defects, negative inotropic and chronotropic effects, and peripheral vasodilation. Intravenous calcium competitively antagonizes these effects and may work synergistically with atropine and catecholamine pressors. Norepinephrine, as an alpha and beta agonist, antagonizes both the negative inotropic effects as well as the peripheral vasodilation that are concomitantly contributing to hypotension. The use of hyperinsulinemic euglycemic therapy has demonstrated efficacy in moribund calcium channel antagonist poisoned patients.

Following acute management and stabilization, GI decontamination must address the sustained release preparations and their potential for prolonged toxicity. Appropriate management includes orogastric lavage, activated charcoal administration, and whole bowel irrigation. Therapy for bradycardia begins with atropine (0.5 to 1 mg IV bolus), followed by 10% calcium chloride or calcium gluconate. Calcium therapy may be repeated to a total dose up to several grams if there is a clinical response. High-dose insulin infusion has been described as a novel treatment for calcium channel poisoning. Insulin has several proposed mechanisms of action including increasing plasma levels of ionized calcium, improving myocardial utilization of carbohydrates, and a positive inotropic effect. Insulin therapy can be initiated with a bolus dose of 0.1 U/kg followed by an infusion of 0.5 mg/kg/h. This infusion can be titrated up to a rate of 1 U/kg/h, with a dextrose infusion to maintain euglycemia. In isolated cases with massive ingestion and poor response to pharmacologic therapy, placement of a transvenous pacer, an intra-aortic balloon pump and extracorporeal membrane oxygenation (ECMO) have each been successful.

COCAINE

Cocaine is a potent sympathomimetic drug commonly abused either by nasal insufflation of cocaine hydrochloride or smoked in the form of “crack” cocaine. Cocaine readily crosses the

blood-brain barrier and has a rapid onset of action. Patients with acute intoxication may complain of chest pain or agitation and may be hypertensive, tachycardic, hyperthermic, and agitated. Seizures are not uncommon. Pulmonary toxicity may result in bronchospasm, pneumothorax, or pneumomediastinum as well as diffuse alveolar hemorrhage. "Crack lung" is the combination of diffuse alveolar infiltrates, eosinophilia, and fevers. Upper airway injuries can occur secondary to thermal effects including uvulitis and epiglottitis. Wide complex dysrhythmias occur secondary to QRS and QT prolongation mediated by sodium channel blockade comparable to types IA and IC antidysrhythmic drugs. Case reports have illustrated successful treatment with sodium bicarbonate therapy. Rhabdomyolysis is also common, and a creatine phosphokinase (CPK) level should be checked and trended. Treatment of acute overdose includes supportive care, rapid cooling for hyperthermia, and benzodiazepines for treatment of seizures and agitation.

Special consideration should be given to body stuffers and body packers. Body stuffers tend to ingest drugs hastily because of a fear of arrest. Body packers ingest large quantities of drugs that are carefully packaged for drug trafficking and face greater potential toxicity in the presence of package leakage or rupture. The onset of altered mental status, seizures, or hypertension heralds rapid absorption of "pure" cocaine, and emergent surgery for gut decontamination is indicated. Asymptomatic body packers can be identified by abdominal radiographs or contrast abdominal computed tomography (CT) scans. Asymptomatic body stuffers and packers should be given multiple doses of activated charcoal to decrease potential cocaine absorption followed by whole bowel irrigation for body packers until all of the packets have been passed. A follow-up contrast study can help confirm that the gut has been cleared of retained packets.

OPIOIDS: HEROIN, FENTANYL, AND METHADONE

Heroin overdoses are a frequent cause of EMS calls as well as ED visits requiring the opioid antagonist naloxone to reverse life-threatening respiratory depression. When faced with the triad of respiratory depression, pinpoint pupils, and lethargy or coma, the administration of small doses of naloxone starting at 0.05 to 0.4 mg IV will induce reversal of respiratory depression and can be followed by larger doses if a desired response (arousal, increased respirations) occurs. Caution should be used in patients deemed opioid tolerant such as heroin users or chronic pain patients in that abrupt reversal may precipitate withdrawal (vomiting, agitation) and in some cases may not improve mental status when other CNS depressants (alcohol, benzodiazepines) are co-ingested. Thus, vomiting can occur while the patient remains sedated and aspiration can result.

Long-acting opioids such as methadone or sustained release morphine or oxycodone may result in recurrent opioid toxicity. In these cases, a continuous naloxone infusion can be initiated because a bolus dose of naloxone will not sustain reversal relative to the longer duration of action of the opioid. These patients will need ICU admission and should be observed for recurrent toxicity for a period after the naloxone infusion is stopped. Patients who are unresponsive and cyanotic after an opioid overdose and then revived with naloxone are at some risk for acute lung injury. Dyspnea may develop within a few minutes to few hours, and a chest radiograph will show pulmonary edema. This can be treated with supplemental oxygen, non-invasive ventilation (Chapter 3), or, rarely, intubation.

DIGOXIN

Although the mortality rate of digoxin poisoning has dramatically improved with the use of digoxin-specific antibody fragments (Digibind), both acute and chronic digoxin poisoning continues to occur. Patients with acute digoxin poisoning may present with emesis and brady- or tachydysrhythmias. Chronic digoxin toxicity often occurs when a patient develops a decrease in renal function, decreasing digoxin clearance by the kidneys. GI symptoms are less prominent, and, instead, slight changes in mental status and visual disturbances as well as bradycardia may occur.

Following acute stabilization of a patient with potential digoxin toxicity, oral-activated charcoal should be administered. Immediate serum potassium and digoxin levels should be obtained and electrocardiographic monitoring should be initiated. Bradycardia, conduction defects, ventricular ectopy, bidirectional ventricular tachycardia, and atrial tachycardia or atrial fibrillation (but without rapid ventricular response) may be seen with digoxin poisoning. Any dysrhythmia is an indication for Digibind therapy. If Digibind is not immediately available, atropine can be given for bradycardia. Potassium elevations > 5 mEq/L indicate significant toxicity and reflect digoxin-induced inhibition of the Na^+/K^+-ATPase pump. This is used as a surrogate marker for toxicity, and treatment with Digibind is indicated as well. In the setting of an unknown overdose with bradycardia when the differential diagnosis includes calcium channel blockers, beta-blockers, and digoxin, patients should be treated with Digibind *before* they are treated with calcium because calcium can significantly and sometimes lethally exacerbate digoxin poisoning.

ORAGANOPHOSPHATES

Organophosphates are commonly used as insecticides, include diazinon, malathion, parathion and chlorpyrifos. Exposures can occur from occupational exposure in agriculture or military use in chemical warfare. Organophosphates bind irreversibly to inhibit the enzyme acetylcholinesterase, thereby increasing acetylcholine at nerve synapses and overstimulating the nicotinic and muscarinic receptors. Clinical presentation depends on the specific agent, dose, and route of exposure. Poisoned patients present with CNS effects ranging from restlessness to delirium, coma, and seizures. The classic cholinergic toxidrome includes salivation, lacrimation, diaphoresis, urinary incontinence, emesis, and bradycardia. An intermediate syndrome can occur 1 to 4 days after an exposure that presents with muscle weakness without cholinergic findings.

The diagnosis of organophosphate poisoning depends on the clinical symptoms and history. Usually, serum tests are not available in a clinically relevant time frame. Treatment consists of airway control, supportive measures and decontamination. These patients have excessive airway secretions and bronchospasm and may require endotracheal intubation. Use only nondepolarizing neuromuscular antagonists (such as rocuronium) to prevent prolonged paralysis. Atropine, a competitive antagonist of acetylcholine, is used to reverse the excessive cholinergic state. The dose is titrated to drying of bronchial secretions, and large doses may be necessary. Atropine will not reverse muscle weakness. Following atropine therapy, consider pralidoxime as an adjunct therapy in severe organophosphate poisoning.

PSYCHOTROPIC MEDICATIONS

Cyclic Antidepressants

Cyclic antidepressants continue to produce significant toxicity in overdose. Screen all overdose patients by electrocardiography for possible cyclic antidepressant ingestion. Prolongation of QRS duration (> 100 msec) is associated with serious toxicity. In one early study, one third of patients with QRS duration > 100 msec had a seizure, and half of those with a QRS greater than 160 msec had a dysrhythmia. A positive deflection of the R wave in lead aVR and an S wave in leads I and aVL are also clues to the presence of a cyclic antidepressant.

Patients with cyclic antidepressant ingestions may present with lethargy and anticholinergic signs such as tachycardia, dry mouth, dilated pupils, decreased bowel sounds, and urinary retention. Seizures, dysrhythmias, or both signify serious cyclic antidepressant ingestion. Patients with recent ingestions (within the prior 30 to 90 minutes) may be asymptomatic initially but rapidly deteriorate in the first hour in the emergency department. Initiate orogastric lavage and activated charcoal early. Obtundation often mandates endotracheal intubation. If the QRS is > 100 msec, give a trial

of sodium bicarbonate (IV bolus followed by infusion) with a goal of alkalinization of the serum to pH 7.45 to 7.55. Alkalinization decreases drug binding to the myocardium, expands the plasma volume, and overcomes the sodium channel blocking type IA cardiotoxic effects induced by the cyclic antidepressant. Use benzodiazepines to treat seizures because a resultant lactic acidosis will exacerbate the cardiotoxicity. If hypotension persists despite sodium bicarbonate and other fluid therapy, a direct vasoconstrictor such as norepinephrine will be more effective than indirectly acting vasopressors.

Lithium

Lithium toxicity differs from other psychotropic drug toxicity. Acute lithium ingestions produce considerable vomiting and diarrhea. As dehydration ensues, renal lithium excretion decreases because lithium, a cation, is reabsorbed with sodium in the proximal tubule. Measure lithium levels, serum electrolytes, and renal function. Because lithium does not bind to activated charcoal, consider orogastric lavage for recent ingestions, followed by whole bowel irrigation to limit distal GI absorption. Vigorous volume expansion with normal saline enhances lithium excretion. Although sodium polystyrene sulfonate (SPS), Kayexalate, has been proposed as a binder of lithium, concerns about inducing hypokalemia limit its use. Patients on chronic lithium therapy can become ill with elevated lithium levels after a new medication (especially diuretics) or an intercurrent GI illness induces dehydration and a change in renal lithium clearance.

The principal toxicity of lithium is to the CNS in both acute and chronic exposures. Patients with acute ingestions will have some GI symptoms initially, followed by neuromuscular manifestations such as hyperreflexia, fasciculations, choreoathetosis, nystagmus, clonus, and lethargy to coma as toxicity progresses. Acute ingestions manifest elevated serum levels, reflecting rapid absorption yet slow distribution to intracellular compartments and the CNS. Therefore, patients may initially be asymptomatic despite high serum levels. During this time, lithium is most accessible to dialysis. Any patient with lithium levels > 4 mEq/L should undergo hemodialysis, as renal elimination is insufficient to prevent significant neural accumulation of lithium. Any patient with serious neurologic symptoms (altered mental status, seizures, or coma) from lithium should also undergo hemodialysis. A lithium level immediately after hemodialysis and 6 hours later should be measured because some patients may need a second treatment after lithium redistributes into the serum from the intracellular space. Unfortunately, not all patients with elevated levels and neurologic signs recover fully, even with hemodialysis.

SALICYLATES

Salicylates are commonly found in many over-the-counter analgesics and combination cold preparations. Other agents such as methyl salicylate (oil of wintergreen), liniments, and products used for vapor rubs all contain salicylates.

Acute salicylate toxicity often manifests with vomiting and auditory disturbances (tinnitus, hearing loss). Hyperpnea or tachypnea may contribute to the classic mixed acid-base disturbance of a primary respiratory alkalosis and a metabolic acidosis (Chapter 83). Severe hyperthermia and diaphoresis may occur. Agitation or confusion may occur and progress to seizures with higher salicylate levels. A serum salicylate level should be obtained early and followed serially to determine the extent and course of the ingestion.

GI decontamination of salicylate-poisoned patients may include orogastric lavage, but most can be effectively treated with multiple doses of activated charcoal. Urinary alkalinization should be performed in any symptomatic patient until the salicylate level is less than 30 to 40 mg/dL. Alkalinization effectively traps the salicylate ion away from the CNS and preserves

availability for renal excretion. Adding three ampules of sodium bicarbonate (44 mEq/ampule) to 1 L of 5% dextrose in water (D5W) infused IV at a rate of 200 to 300 mL/h alkalinizes the urine. Hypokalemia commonly complicates alkalinization and should be corrected prior to initiating. Because salicylate poisoning is commonly accompanied by fluid losses (vomiting, sweating, tachypnea), the saline load is usually well tolerated. However, cerebral edema and salicylate-induced acute lung injury may complicate alkalinization therapy, especially in elderly patients.

In general, levels > 100 mg/dL mandate hemodialysis. Rapidly rising levels, severe acid-base disturbances, neurologic complications, or volume overload precluding alkalinization may also require hemodialysis. Early consultation with a nephrologist is advisable in any significant salicylate poisoning.

SEDATIVES

Benzodiazepines

Benzodiazepines are a surprisingly safe drug for sedation, causing dose-dependent CNS depression. Unlike barbiturates, however, first-generation benzodiazepines (diazepam, chlordiazepoxide) have only rarely been associated with significant respiratory or cardiovascular depression. However, all benzodiazepines may produce life-threatening CNS and respiratory depression when ingested along with large amounts of ethanol or other sedative-hypnotic agents. As with barbiturates, benzodiazepine dependence is also common, and withdrawal may present as a severe delirium tremens–like syndrome.

Laboratory testing by qualitative immunoassay is widely available. Many rapid screens use oxazepam as the immunoreagent, and therefore some of the newer benzodiazepines that are not metabolized to oxazepam go undetected. Management of benzodiazepine toxicity is supportive, with no proven benefit for enhanced elimination. The role of a specific antagonist, flumazenil, in overdose management is controversial. Because its effect is brief (1 to 2 hours) and its use may precipitate seizures (in a benzodiazepine-dependent patient or with concomitant cocaine or cyclic antidepressant ingestion), avoid flumazenil in patients admitted to the ICU.

GHB (γ-Hydroxybutyrate)

γ-Hydroxybutyrate (GHB) has been used as an anesthetic, a therapy for narcolepsy, and a treatment for ethanol and opioid withdrawal; however, it has also been abused as a recreational drug. GHB is usually abused in the setting of dance parties or nightclubs. After ingestion, GHB is rapidly absorbed and acts in the CNS at gamma aminobutyric acid (GABA) and opioid receptors. The hallmark of poisoning is deep sedation, followed by unusually fast resolution to normal mental status. Significant respiratory depression may require ventilatory support; modest bradycardia is often present. Myoclonic motion of the face and extremities is sometimes noted. Reversal agents such as naloxone and flumazenil are not effective. Treatment is supportive, and patients usually recover within a few hours without sequelae.

SEROTONERGIC AGENTS

Serotonin syndrome (SS) is a complication of serotonergic agents, which are most commonly available as the newer, safer antidepressants and increase serotonin in the CNS. Although SS may occur after an overdose of such an agent, more often SS occurs soon after an increase in dose of a primary serotonergic agent or the addition of a second agent. Serotonergic drugs are legion, including selective serotonin reuptake inhibitors, such as fluoxetine, tricyclic antidepressants, monoamine oxidase (MAO) inhibitors, amphetamines such as "Ecstasy" (3,4-methylenedioxymethamphetamine or MDMA), and opioids such as meperidine, tramadol, and dextromethorphan.

SS is a challenge to diagnose because it has no confirmatory laboratory tests, and signs and symptoms vary in diversity and severity. Common clinical manifestations include one or more of the following: (1) altered mental status, from restlessness to agitation, or unresponsiveness; (2) autonomic nervous system dysfunction, such as hyperthermia, tachycardia, diaphoresis, and hypo- or hypertension; and (3) neuromuscular dysfunction, such as myoclonus, muscle rigidity, and hyperreflexia (especially of the lower extremities). SS can result in lactic acidosis, rhabdomyolysis, renal and hepatic dysfunction, or the acute respiratory distress syndrome, but generally it has a good prognosis. Treatment remains supportive with aggressive cooling and sedation with benzodiazepines. All serotonergic agents should be discontinued.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 58

Acute Pancreatitis

Douglas O. Faigel ■ Laura Wolfe ■ Faten N. Aberra

Acute pancreatitis (i.e., acute inflammation of the pancreas) has multiple causes and may manifest as mild disease or a life-threatening disorder that can result in multiple organ system failure, sepsis, and death. Acute pancreatitis typically presents as abdominal pain, in association with elevated blood levels of pancreatic enzymes. It may occur as an initial or recurrent attack. The pathogenesis is considered to be pancreatic autodigestion caused by intraparenchymal activation and release of proteolytic enzymes from zymogen granules. The resultant destruction and inflammation can produce a variety of local complications for which a clinically based system of classification and terminology has been developed (Table 58.1).

Etiology

More than 90% of cases of acute pancreatitis are due to ethanol abuse or cholelithiasis or are idiopathic. A variety of other agents, including medications and toxins, account for the remaining 10% (Box 58.1 and Table 58.2). Biliary microlithiasis (which is bile containing small crystals of cholesterol monohydrate, calcium bilirubinate, or calcium carbonate) is also recognized as a cause of acute and recurrent pancreatitis, accounting for up to 30% of pancreatitis previously considered idiopathic.

Clinical Presentation

The hallmark of acute pancreatitis is abdominal pain associated with elevated blood levels of pancreatic enzymes. The pain generally comes on suddenly and rises to a peak within a few hours. It is steady, typically midepigastric, and bores through to the back. The patient prefers to remain still in bed and may assume a hunched-over or semifetal position in an attempt to release tension on the retroperitoneum; exaggerating the lumbar lordosis exacerbates the pain. Nausea and vomiting are present in more than 80% of patients. The presence of bluish discolorations of the flanks (Grey Turner sign) or periumbilical area (Cullen sign) is rare and does not occur at presentation but rather may develop several days into the illness because of dissection of peripancreatic bleeding into the subcutaneous tissues. Bowel sounds are diminished, or absent if a paralytic ileus is present. An abdominal radiograph may reveal a *sentinel loop*, which is a paralyzed air-filled segment of proximal small bowel in close proximity to the inflamed pancreas. The abdomen is typically soft but with exquisite tenderness to deep palpation. Peritoneal signs may be present in complicated cases. Subcutaneous fat necrosis may be present and resembles erythema nodosum or panniculitis. Altered mental status may be due to shock or complications of chronic alcoholism (e.g., alcohol withdrawal syndrome [AWS; Chapter 31], delirium tremens, and Wernicke-Korsakoff syndrome).

The serum amylase level rises in acute pancreatitis within 2 to 12 hours of the onset of symptoms and remains elevated for 3 to 5 days. Persistently raised levels suggest local complications. The lipase level may remain elevated longer than the amylase level. Elevation of both enzymes to levels greater

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TABLE 58.1 ■ **Classification System for Acute Pancreatitis**

Term	Definition	Comments
Severe acute pancreatitis	Acute pancreatitis associated with organ failure, certain local complications (necrosis, abscess, or pseudocyst), or both. Most often it represents the development of *pancreatic necrosis.*	Early prognostic signs for severe disease: three or more Ranson criteria (see Table 58.4) or eight or more points in the APACHE II system.*
Acute fluid collections	These collections, localized in or near the pancreas, occur early in the course of acute pancreatitis and always lack a defined wall.	They are common, occurring in 30%–50% of patients with severe pancreatitis, and most regress spontaneously. Those persisting represent an early stage in the development of acute pseudocysts and pancreatic abscesses.
Pancreatic necrosis	Diffuse or focal area(s) of nonviable pancreatic parenchyma, typically associated with peripancreatic fat necrosis. Pancreatic necrosis may be sterile or become infected (the latter triples the risk of death).	Dynamic contrast-enhanced computed tomography shows a well-marginated zone of nonenhancement.
Acute pseudocysts	Collections of pancreatic fluid, enclosed by a defined wall of fibrous or granulation tissue, arising from acute pancreatitis. They are usually rich in pancreatic enzymes and most often sterile.	Sometimes palpable but most often discovered by imaging studies, which show a well-defined wall. They form 4 or more weeks from the onset of acute pancreatitis.
Pancreatic abscesses	Circumscribed intra-abdominal collections of pus, in or near the pancreas, but containing little or no pancreatic necrosis. Do *not* use this term to describe *infected pancreatic necrosis* (the latter has twice the mortality risk of a pancreatic abscess).	These occur 4 or more weeks after the onset of acute pancreatitis and likely arise as a result of limited necrosis with subsequent liquefaction and infection.
Pancreatic ascites	The presence of free fluid with pancreatic enzymes inside the peritoneal cavity.	Pancreatic ascites may be sterile or infected.
Infected pseudocyst	Variably used to describe infected pancreatic necrosis or pancreatic abscesses.	Avoid use of this ambiguous term.
Hemorrhagic pancreatitis	Defined by direct visualization of hemorrhage in the gland.	Incorrectly used as a synonym for *pancreatic necrosis,* which may not be hemorrhagic.
Pancreatic phlegmon	Originally referred to a palpable mass of sterile edematous tissues, but later used to describe pancreatic necrosis with infection.	Avoid use of this ambiguous term.

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than 10 times the upper limit of normal is highly specific but only 80% to 90% sensitive for acute pancreatitis. Levels less than 3 times the upper limit of normal should be considered non-specific.

Differential Diagnosis

There are multiple causes for an elevated pancreas enzyme level other than acute pancreatitis (Box 58.2). Several deserve special comment. Perforated peptic ulcer may present with pain and elevated pancreatic enzymes resulting from spillage into the peritoneal cavity. Abrupt onset of pain,

BOX 58.1 ■ Selected Causes of Acute Pancreatitis

Major Causes (~90% of cases)

Ethanol abuse
Gallstones, including microlithiasis
Idiopathic

Other Causes (~10% of cases)

Medications and toxins (see Table 58.2)
Metabolic conditions
—Hyperlipidemia
—Hypercalcemia
—End-stage renal failure
—Hypothermia
Infections
—Viral (mumps, Coxsackie virus, hepatitis A or B, echovirus, adenovirus, cytomegalovirus, varicella, Epstein-Barr virus, human immunodeficiency virus)
—Bacterial *(Mycoplasma pneumoniae, Salmonella, Campylobacter jejuni, Mycobacterium, Legionella, Leptospira)*
—Intraductal parasites *(Ascaris, Clonorchis)*
Trauma
—Blunt
—Postoperative (especially after intra-abdominal surgery or cardiopulmonary bypass)
—Endoscopic retrograde cholangiopancreatography (ERCP)

TABLE 58.2 ■ **Medications and Toxins Associated with Acute Pancreatitis**

Category	Definite Association	Probable Association
Antihypertensive agents		ACE inhibitors
		Methyldopa
Anti-inflammatory and analgesic agents		Acetaminophen
		Corticosteroids
		Mesalamine
		NSAIDs
		Salicylates
Anti-infective agents	Didanosine (ddI)	Erythromycin
	Pentamidine	Metronidazole
	Sulfonamides	Nitrofurantoin
	Tetracyclines	
Chemotherapeutic agents	6-MP, azathioprine	
	L-Asparaginase	
Diuretics	Furosemide	Chlorthalidone
	Hydrochlorothiazide	Ethacrynic acid
Toxins	Ethanol	
	Methanol	
Others	Estrogens (via hyperlipidemia)	
	Intravenous lipid infusions	
	Valproic acid	

6-MP, 6-mercaptopurine; NSAIDs, nonsteroidal anti-inflammatory drugs; ACE, angiotensin-converting enzyme.

BOX 58.2 ■ Selected Nonpancreatitis Causes of Hyperamylasemia

Intra-abdominal emergencies
- —Perforated viscus (stomach, duodenum, jejunum)
- —Mesenteric infarction
- —Biliary obstruction
- —Acute cholecystitis
- —Ruptured ectopic pregnancy
- —Salpingitis

Salivary adenitis

Poor renal clearance
- —Renal insufficiency
- —Macroamylasemia

Miscellaneous
- —Metabolic, diabetic ketoacidosis
- —Acute and chronic liver disease

peritoneal signs, and free air on radiography differentiates this entity from pancreatitis. Acute cholecystitis may sometimes be associated with mild hyperamylasemia. The pain of cholecystitis is typically right-sided, and ultrasonography or computed tomography can suggest the diagnosis. A stone in the bile duct (choledocholithiasis) may cause cholangitis with biliary colic, elevated liver-associated enzymes, and jaundice with or without concomitant pancreatitis. Bowel ischemia and infarction resulting from mesenteric vascular occlusion, volvulus, and hernia are important considerations because of the need for prompt surgical treatment. Salpingitis and ruptured ectopic pregnancy may cause abdominal pain and elevated amylase levels and may occasionally be confused with acute pancreatitis.

Diagnostic Evaluation

A diagnosis of acute pancreatitis is supported by elevated serum amylase or lipase (≥ 3× upper limit of normal) and abdominal pain. Contrast-enhanced computed tomography (CT) of the pancreas is recommended in patients with severe pancreatitis at 72 hours from admission to evaluate for complications. By contrast-enhanced CT scan, nonenhancing areas within the pancreas correlate with the presence of necrosis. Fluid collections and evidence of inflammation around the pancreas are well seen. A contrast-enhanced CT performed before 72 hours after admission may underestimate the severity of disease, but it can confirm acute pancreatitis in patients where there is clinical uncertainty. Dynamic CT during bolus intravenous (IV) injection of contrast may both provide a diagnosis (by demonstrating inflammation and ruling out other entities) and help with prognosis (by assessing the degree of inflammation and necrosis).

As part of the evaluation for risk factors of acute pancreatitis, laboratory measurements of serum calcium, liver chemistries, and triglycerides should also be obtained. Abdominal ultrasound is recommended to evaluate for underlying cholelithiasis and choledocholithiasis as a cause for pancreatitis. Contrast-enhanced CT scan or endoscopic ultrasound is also recommended in patients over the age of 40 years and without an explanation for acute pancreatitis to evaluate for malignancy.

Prognosis

Severity of disease and prognosis can also be gauged by clinical scoring systems. Ranson and coworkers introduced the first such system in 1974, often referred to as Ranson's criteria (Table 58.3), based on findings on admission to the hospital and at 48 hours after admission. This system has proven to be useful specifically to define those with severe acute pancreatitis (see Table 58.1) and their

TABLE 58.3 ■ **Ranson's Criteria for Severity and Prognosis* in Acute Pancreatitis**

Criteria on Admission	Criteria within 48 Hours of Admission
Age > 55 years	Decrease in hematocrit > 10% (absolute)
WBC > 16,000/μL	BUN increase > 5 mg/dL (1.79 mmol/L)
Glucose > 200 mg/dL [11.1 mmol/L]	Calcium < 8 mg/dL (2 mmol/L)
LDH > 350 IU/L	Pao_2 < 60 mm Hg
AST > 250 U/L	Base deficit > 4 mEq/L (4 mmol/L)
	Fluid sequestration > 6 L

*Predicted mortality for patients with nongallstone pancreatitis: < three criteria, 0% mortality; three to five criteria, 10% to 20% mortality; six or more criteria, > 50% mortality.
AST, aspartate aminotransferase; BUN, blood urea nitrogen; LDH, lactic dehydrogenase; WBC, white blood cell count.
From Ranson JHC, Rifkind KM, Roses DF, et al: Prognostic signs and the role of operative management in acute pancreatitis. Surg Gynecol Obstet 129:69-81, 1974.

TABLE 58.4 ■ **Local and Systemic Complications of Acute Pancreatitis**

System	Complication
Cardiovascular	Hypotension and circulatory shock
	Rupture of pseudoaneurysm
	Splenic rupture or hematoma
Central nervous system	Psychosis
Gastrointestinal	Bowel obstruction (mechanical versus paralytic)
	Gastrointestinal hemorrhage
	Ulceration
	Gastric varices
Hematologic	Coagulopathy (disseminated intravascular coagulation)
Metabolic	Hyperglycemia
	Hypocalcemia
Renal	Acute renal failure
	Right-sided hydronephrosis
Respiratory	Acute respiratory distress syndrome
Vision	Retinopathy

mortality risks. Patients with multiple organ system failure (e.g., hypoxia, renal failure, hypotension) do poorly.

The disease severity evident on CT correlates well with clinical course and outcome. Patients with only interstitial edema of the pancreas on CT usually have a mild clinical course with low risk of local or systemic complications, and recovery is the rule. In contrast, patients with evidence of pancreatic necrosis usually have a high risk of local and systemic complications (Table 58.4) and about a 25% risk of death.

Management

Patients with severe acute pancreatitis require admission to the intensive care unit (ICU) for management by a multidisciplinary team, including an intensivist, a gastroenterologist, and a surgeon.

Determining which patients will develop severe acute pancreatitis may be difficult and the scoring systems used to predict mortality—such as Ranson, APACHE (Acute Physiology and Chronic Health Evaluation), and Glasgow criteria—require at least 48 hours of observation to be accurate. Thus, the Atlanta Symposium has identified clinical factors to define the severity of acute pancreatitis primarily examining for evidence of organ failure and complications. Risk factors for severity include age > 55, obesity (body mass index [BMI] > 30), organ failure at admission, and pleural effusions or pulmonary infiltrates.

Initial management requires supportive care with aggressive intravenous hydration titrating to a normal hematocrit, in an effort to prevent pancreatic necrosis, as well as careful monitoring for organ failure and other systemic complications. The hematocrit should be drawn on admission and 12 hours and 24 hours postadmission. Potential offending medications (see Table 58.2) should be discontinued, and reintroduction should be avoided, as it can lead to fulminant disease. Initially, patients should receive nothing by mouth. Nasogastric suction should be instituted for persistent vomiting, ileus, or obstruction but otherwise does not alter ultimate outcome. Nutritional support should be started when it becomes clear the patient will not be taking oral food for more than 7 days. Studies looking at parenteral versus nasojejunal feeding demonstrate that enteral feeds do not exacerbate pancreatitis and they can decrease the inflammatory response, complications of vascular catheter infections, and episodes of hyperglycemia compared to parenteral nutrition. Elemental or semielemental enteral diets are recommended (Chapter 15). Adequate opioid analgesia is required. There is no benefit of one opioid over another (Chapter 87), but avoid high doses of meperidine (previously felt to be the agent of choice), which may result in seizures, particularly in patients with renal failure.

Primary and prophylactic medical and surgical therapies have been largely unsuccessful, with the exception of gallstone pancreatitis. Therapies designed to rest the pancreas by inhibiting pancreatic secretion with nasogastric suction, histamine H_2-receptor blockers, atropine, glucagon, somatostatin, or fluorouracil do *not* change the course of the disease. Studies have found no benefit in using prophylactic antibiotics. When infected pancreatic necrosis is suspected, obtaining a CT-guided fine-needle aspirate (FNA) is recommended to guide appropriate antibiotic therapy. Early surgical therapies such as peritoneal lavage and pancreatic resection provide no benefit. Surgical treatment of gallstone pancreatitis is not beneficial and when performed in the early acute phase may have a mortality rate as high as 48%. Endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and stone extraction is indicated upon evidence of biliary obstruction caused by a stone (e.g., increasing jaundice) or of acute cholangitis. However, in patients with biliary pancreatitis without signs of obstruction or cholangitis, ERCP and sphincterotomy confer no benefit.

Supportive treatment addresses the systemic and local complications that may occur (see Table 58.3). Shock is a combination of hypovolemic shock from massive third spacing of fluid (as evidenced by hemoconcentration), and distributive shock due to severe systemic inflammatory response syndrome (SIRS). Cardiovascular collapse may cause early death in patients with severe pancreatitis, and it requires aggressive volume replacement and vasopressors. Hypoxemia, occurring in a majority of patients during the first 2 days, is generally asymptomatic with a normal chest radiograph and resolves as the pancreatitis improves. However, up to 20% of patients with severe pancreatitis develop the *acute respiratory distress syndrome* (ARDS; see Chapter 73) requiring mechanical ventilation, portending greater than 50% mortality. *Pleural effusions* are usually left-sided and exudative, with high amylase levels; they resolve as the pancreatitis improves. Persistent and large plural effusions may indicate a *pancreaticopleural fistula*. *Coagulopathy*, generally from disseminated intravascular coagulation (DIC), has no specific treatment, but factor replacement may be required for active bleeding or planned invasive procedures. *Acute renal failure* is generally due to acute tubular necrosis from renal hypoperfusion; the need for dialysis also predicts greater than 50% mortality. *Hyperglycemia* transiently

occurs in 50% of patients and, if severe, requires insulin therapy. *Hypocalcemia* is multifactorial because of the saponification of calcium salts in areas of fat necrosis, hypoalbuminemia, hypomagnesemia, and abnormalities of glucagon, calcitonin, and parathyroid hormone secretion or responsiveness. The ionized calcium level should guide treatment of hypocalcemia. *Sudden blindness,* which occurs rarely but may be permanent, arises from Purtscher's angiopathic retinopathy (discrete flame-shaped hemorrhages with cotton-wool spots). *Idiopathic pancreatic encephalopathy* with confusion, delirium, and coma may be due to the effects of brain hypoperfusion and metabolic abnormalities. It must be differentiated from other causes of altered mental status, including the sequelae of alcoholism.

The most common gastrointestinal complication is *paralytic ileus*, treated by nasogastric decompression and observation. Occasionally, mechanical *bowel obstruction* occurs from bowel involvement by the inflammatory process. Mechanical obstruction can also be managed conservatively, although persistence may warrant surgical resection of the affected loop. *Gastrointestinal hemorrhage* may occur from stress ulcerations, bleeding from gastric varices, or a ruptured pseudoaneurysm. Stress ulcerations can be managed endoscopically and with proton pump inhibitors. *Gastric varices* develop as a consequence of splenic vein thrombosis, which may complicate either acute or chronic pancreatitis. Treatment options include endoscopic cyanoacrylate glue injection or splenectomy. Erosion of major peripancreatic arteries, usually in association with a pseudocyst, can produce pseudoaneurysm formation. Bleeding from a ruptured pseudoaneurysm reaches the gastrointestinal tract via the pancreatic duct or directly via the rupture of the pseudocyst into the bowel lumen. *Intra- or retroperitoneal hemorrhage* can also occur. Treatment of this unusual condition is by angiographic embolization or surgery. Extension of pancreatic inflammtion may cause splenic rupture or right-sided hydronephrosis.

Local pancreatic complications include the development of fluid collections, pseudocysts, and localized infection (see Table 58.1), primarily in patients with necrotizing pancreatitis. Sterile fluid collections can be managed expectantly because most will resolve. Ten percent to 15% of patients will acquire pseudocysts, and two thirds of these will resolve spontaneously, generally within 6 weeks. Complications of pseudocysts include pain, bleeding, infection, bowel obstruction, and rupture. Endoscopic, percutaneous, or surgical therapy is indicated for symptomatic matured (may take at least 4 weeks) pseudocysts. Traditional treatment of pancreatic abscesses and infected pancreatic necrosis with surgical drainage and systemic antibiotics is being supplanted with endoscopic transgastric drainage and/or percutaneous drainage. In patients with acute pancreatitis who improve with supportive treatment, no further therapy is needed. However, with no clinical improvement or further deterioration, consider severe sterile or infected necrosis absent obvious local or systemic complications. Both sterile and infected necrosis may produce fever and leukocytosis (> 20,000/μL). Although no consensus exists for the role of surgery in severe sterile necrosis, most experts recommend extensive surgical debridement for infected necrosis. However, differentiating sterile from infected necrosis may be challenging. Intrapancreatic air on CT indicates the presence of gas-forming organisms and the need for surgery. CT-guided fine-needle aspiration for Gram stain and culture is both highly sensitive and specific for infection, with Gram stain by itself being 98% sensitive.



An annotated bibliography can be found at www.expertconsult.com.

Pearls

- Initial assessment is aimed at determining the cause and differentiating mild from severe disease based on prognostic signs and CT findings.
- Patients with severe pancreatitis require admission to the ICU, aggressive fluid resuscitation, treatment of systemic complications, and ERCP if signs of biliary obstruction or acute cholangitis are present.
- In patients with necrotizing pancreatitis who do not improve or deteriorate while on medical therapy, the presence of infected necrosis should be considered, and CT-guided aspiration should be contemplated.
- Patients with infected necrosis should receive antibiotics and undergo debridement or another drainage procedure.
- Those with sterile necrosis who do not improve despite prolonged medical therapy may benefit from late drainage or surgery.

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CHAPTER 59

Acute Liver Failure

Karen L. Krok

In acute liver failure (ALF) there is rapid deterioration of liver function in a previously healthy individual. By definition there is evidence of coagulopathy (International normalized ratio, INR ≥ 1.5) and mental status alteration (encephalopathy) in a patient without preexisting cirrhosis within 26 weeks of the onset of jaundice. ALF has been subdivided into hyperacute (illness < 7 days), acute (illness between 7 to 21 days), and subacute (illness between 21 days and 26 weeks), but these subdivisions have not shown any prognostic significance distinct from the etiology of the liver failure.

The presentation of ALF is rapid, dramatic, and frequently leads to coma and death from cerebral edema and multiorgan failure over the course of a few days. There are approximately 2000 cases of ALF in the United States on a yearly basis. It is a rare indication for liver transplantation, accounting for only 6% of all liver transplants. One-year survival after liver transplantation is 82%, which is lower than the 88% 1-year survival rate seen in all other recipients, probably owing to the higher severity of illness at the time of transplant. Once listed for a liver transplant, patients will wait an average of 3.5 days and 22% of patients will die waiting for a transplant. With only medical management in an intensive care unit (ICU) there is a 25% to 43% transplant-free and spontaneous recovery rate. For this reason, when there is concern for ALF, patients should be immediately transferred to a transplant center where an evaluation for a transplant can begin.

Etiology of Acute Liver Failure

The prognosis of ALF is dependent on its etiology, so every effort should be made to look for the underlying cause of the liver injury (Table 59.1). However, up to 20% of cases will have no discernable cause. The most common cause of ALF in the United States is acetaminophen toxicity, most recently accounting for approximately 39% to 50% of all cases of ALF. Idiosyncratic drug reactions account for 13% of cases of ALF. Viral hepatitis (acute hepatitis A and B combined) has become a less frequent cause of ALF in the United States, accounting for only 12% of all cases. Acute hepatitis C does not appear to lead to ALF. Hepatitis E is a significant cause of liver failure in endemic countries (Russia, Pakistan, Mexico, and India) and should be considered in any patient who travels to these countries and in any pregnant woman, as hepatitis E has a more severe course during pregnancy.

Wilson disease and autoimmune hepatitis account for 3% and 4% of all cases of ALF, respectively, and are unique in that patients can still be considered as having ALF even though there is a preexisting chronic liver disease if the disease previously had been unrecognized. Mushroom toxicity (usually *Amanita phalloides*) may cause ALF, and the initial history should always include recent mushroom ingestion. Acute fatty liver of pregnancy and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome (Chapter 72) typically occur during the third trimester, and prompt delivery of the fetus is essential to achieve good outcomes.

Additional online-only material indicated by icon.

TABLE 59.1 ■ **Causes of Acute Liver Failure**

Category	Examples
Drugs	Acetaminophen, halothane, phenytoin
Miscellaneous	Acute fatty liver of pregnancy, Reye syndrome, Wilson disease, malignant infiltration, autoimmune hepatitis
Toxins	*Amanita phalloides,* carbon tetrachloride
Vascular	Budd-Chiari syndrome, cocaine, heat stroke, ischemia ("shock liver"), veno-occlusive syndrome
Viral hepatitis	Hepatitis A, B, D, E, C,* G,* CMV, HSV, EBV, varicella

*Uncertain cause of acute liver failure.
CMV, cytomegalovirus; HSV, herpes simplex virus; EBV, Epstein-Barr virus.

Diagnosis and Initial Evaluation

All patients with clinical or laboratory evidence of moderate to severe acute hepatitis should have a prothrombin time measured and be assessed for subtle alterations in mentation. An INR ≥ 1.5 and evidence of encephalopathy mandate a hospital admission, preferably to an ICU given the potential for rapid clinical deterioration.

History taking should include a careful review of possible medication overdoses (especially acetaminophen and acetaminophen-containing products), medications newly started within the last 6 months, toxins (*Amanita phalloides* mushrooms in particular), herbal supplements, and risk factors for exposure to an acute viral hepatitis. Physical examination should focus on any stigmata of chronic liver disease; the prognosis is improved in a patient with acute on chronic liver injury compared to a patient with ALF alone. Observe patients frequently for the development of hepatic encephalopathy; once grade I or II encephalopathy has developed, transfer patients to a transplant center as they may deteriorate rapidly (Table 59.2).

Initial laboratory examination must be extensive and include tests to evaluate for the severity and etiology of the ALF (Table 59.3). Plasma ammonia (venous or arterial), although not very useful in patients with chronic liver disease, can help determine the risk for cerebral herniation in patients with ALF. Although no definite threshold ammonia level has been established, patients with arterial ammonia levels > 200 mcg/dL have a significant risk (close to 100%) of developing severe hepatic encephalopathy and a 55% risk of developing increased intracranial pressure. The utility of a liver biopsy is marginal, as it will usually not change therapy; if indicated, it is typically done via the transjugular approach because of a patient's coagulopathy.

Hepatic cross-sectional imaging or Doppler ultrasound is important in the diagnosis of ALF. Not only will it look at the hepatic parenchyma and give some information as to the presence of any chronic liver disease (nodular liver, presence of varices, splenomegaly), but it also will look at the patency of the hepatic veins to exclude Budd-Chiari syndrome.

Wilson disease requires special consideration, as it may be difficult to diagnose because the low ceruloplasmin levels that are characteristic of the disease are present in most patients with ALF, regardless of etiology. Kaiser-Fleischer rings are not uniformly present and serum copper levels require several days to obtain. In these cases, a very low alkaline phosphatase with a marked hyperbilirubinemia resulting from profound hemolytic anemia is relatively specific for Wilson disease. An alkaline phosphatase-to-total bilirubin concentration less than 4 is consistent with Wilson disease and may aid in the diagnosis. Rapid diagnosis is essential; these patients will require a liver transplant as spontaneous recovery is estimated at 0%.

TABLE 59.2 ■ **Grading Scale for Hepatic Encephalopathy**

Grade	Symptoms	Signs	Electroencephalographic Findings
I	Subtle change in mental status, difficulty in computation, emotional lability	No asterixis	Normal or symmetric slowing, triphasic waves
II	Drowsy, unequivocal loss of computation, memory loss	Asterixis	Abnormal symmetric slowing, triphasic waves
III	Sleepy but arousable, can answer simple questions only	Asterixis (if able to comply)	Abnormal symmetric slowing, triphasic waves
IVa	Coma, no response to commands, responds to pain	Unable to comply for asterixis testing, Babinski reflex is present	Abnormal slow delta waves (2–3/min)
IVb	Coma, no response to commands or pain	Same as in IVa	Same as in IVa

TABLE 59.3 ■ **Initial Laboratory Analysis**

Acetaminophen level
Ammonia level
Arterial blood gas
Autoimmune markers: ANA, ASMA, immunoglobulin levels
CBC
Ceruloplasmin level
Comprehensive panel
HIV
Pregnancy test (females)
Prothrombin time/INR
Toxicology screen
Type and screen
Viral hepatitis serologies: anti-HAV IgM, HepBsAg, anti-HepBcore IgM, HCV Ab

ANA, anti-nuclear antibody; anti-HepBcore, antihepatitis B core antibody; ASMA, anti-smooth muscle antibody; CBC, complete blood count; HAV, hepatitis A virus; HCV Ab, hepatitis C virus antobody; HepBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; IgM, immunoglobulin M.

Predicting Prognosis in Acute Liver Failure

Accurate prognosis of ALF is a paramount goal. The traditional King's College Hospital criteria have been the most commonly used and most frequently validated prognostic criteria for ALF (Table 59.4). Several studies have shown a positive predictive value from 70% to 100% and a negative predictive value of 25% to 94% for the King's College Hospital criteria for determining mortality. An Acute Physiology and Chronic Health Evaluation (APACHE) II score greater than 15 on admission has a specificity of 92% and sensitivity of 81% for predicting a patient's mortality.

Other prognostic criteria have been proposed, including alpha-fetoprotein (a rising level over the first 3 days is a predictor of survival) and serum phosphate levels (hyperphosphatemia is found in nonsurvivors). The Model for End-stage Liver Disease (MELD) score, now widely used to predict mortality among patients with chronic liver disease, has been studied to predict mortality in ALF. As a predictor of death from ALF, the MELD score does not provide more information

TABLE 59.4 ■ **Prognostic Criteria Predicting Need for Liver Transplantation**

Acetaminophen Toxicity

pH < 7.3 (irrespective of grade of encephalopathy) *or* prothrombin time > 100 sec and serum creatinine level > 3.4 mg/dL (300 μmol/L) in patients with grade III or grade IV encephalopathy

All Other Causes

Prothrombin time > 50 sec (irrespective of encephalopathy) *or* any three of the following variables (irrespective of grade of encephalopathy):

—Age > 40 years

—Liver failure because of drug idiosyncrasy or idiopathic hepatitis previously called NANB

—Duration of jaundice prior to encephalopathy > 7 days

—Prothrombin time > 25 sec

—Serum bilirubin > 17.5 mg/dL (300 μmol/L)

NANB, non-A, non-B.

than the King's College Hospital criteria. Overall, all current scores miss accuracy in predicting mortality from ALF. In general, the clinical course of encephalopathy is regarded as the most informative datum in a particular patient—the deeper the coma, the worse the outcome.

The etiology of the ALF is the most significant predictor of outcome. Patients with ALF resulting from acetaminophen, hepatitis A, shock liver, or pregnancy-related disease have a > 50% transplant-free survival rate, whereas all other etiologies have a < 25% transplant-free survival rate. Renal failure and acidosis (particularly in acetaminophen-induced ALF) are particularly ominous signs.

Management of Patients with Acute Liver Failure

All patients with ALF should be transferred to an ICU at a liver transplant center early in their disease course. Early transfer of patients with *any* degree of encephalopathy is crucial.

SPECIFIC THERAPY

Patients with ALF who have ingested acetaminophen should receive a full course of *N*-acetylcysteine (NAC). Treatment with NAC should be instituted even if 24 to 36 hours have elapsed since the ingestion of acetaminophen (Chapter 57). NAC can be administered intravenously or orally. The intravenous dose is a loading dose of 150 mg/kg in 5% dextrose over 15 minutes, followed by a maintenance dose of 50 mg/kg given over 4 hours followed by 100 mg/kg administered over 16 hours. The oral dose is 140 mg/kg by mouth or via nasogastric tube, followed by 70 mg/kg by mouth every 4 hours for a total of 17 doses. In addition, some studies suggest that NAC may have beneficial effects on ALF from causes other than acetaminophen.

Penicillin G and silibinin (silymarin or milk thistle) are accepted antidotes for *Amanita phalloides* poisoning, although there is no controlled trial establishing their efficacy. Silymarin has been given in average doses of 30 to 40 mg/kg/day (either intravenously or orally) for an average duration of 3 to 4 days.

Pregnancy-related ALF is treated by prompt delivery of the fetus.

HYPOGLYCEMIA

ALF, especially when caused by acetaminophen or one of the microvesicular fat deposition disorders (acute fatty liver of pregnancy), is often complicated by hypoglycemia. Patients should have their

glucose level checked at least every 2 hours. An intravenous glucose infusion (1.5 to 2 g/kg/day) is recommended in patients who develop hypoglycemia.

COAGULOPATHY

Do not give fresh frozen plasma simply to correct a prolonged prothrombin time. The uncorrected prothrombin time is a useful parameter to monitor recovery or deterioration of hepatic synthetic function; along with a patient's mental status, the prothrombin time is the most significant marker. Correct coagulopathy by fresh frozen plasma before invasive procedures, such as placement of central venous catheters or an intracranial pressure (ICP) monitor, or whenever there is evidence of serious hemorrhage.

HEPATIC ENCEPHALOPATHY AND HYPERAMMONEMIA

Lactulose is given to all patients with hepatic encephalopathy. Its benefit is maximal when the patient is passing three to four soft stools per 24 hours. Nonabsorbable antibiotics (Flagyl, neomycin, rifaximin), like lactulose, have never been proven to be beneficial in ALF but now are prescribed widely to aid in the treatment of encephalopathy. Avoid neomycin because of the risk of renal injury.

ALF is a catabolic state. No convincing controlled clinical trials support withholding protein completely or administering specially formulated oral or parenteral amino acid feedings.

INFECTION PROPHYLAXIS AND SURVEILLANCE

Infection is one of the principal causes of death in patients with ALF. The most common site of infection is the lung, followed by the urine and bloodstream. The most commonly isolated organisms are gram-positive cocci and enteric gram-negative bacilli, but fungal infections are present in up to 30% of patients with ALF. Prophylactic antibiotics have not been shown to improve outcome or survival in patients with ALF. Consider empiric antibiotics in patients with stage IV encephalopathy, the presence of systemic inflammatory response syndrome, persistent hypotension, or upon listing for a liver transplant. Which antibiotic to choose is always difficult to determine, but a broad-spectrum antibiotic, like a third-generation cephalosporin, is a reasonable option. Add vancomycin in patients colonized with methicillin-resistant *Staphylococcus aureus* or indwelling catheters. Start an antifungal agent in any patient whose signs of infection do not promptly improve after starting an antibacterial agent.

SEDATION

Psychomotor agitation and pain both can contribute to an increase in intracranial pressure and should be avoided. There are insufficient data to recommend one standard agent for sedation in patients with ALF. Propofol, though, has a shorter half-life than commonly used benzodiazepines and decreases cerebral blood flow (thereby lowering intracranial pressure [see Chapter 41]), so it is the recommended agent. Fentanyl is the agent of choice to treat pain as it has a short half-life.

HYPOTENSION

As in all patients, volume resuscitation should first be attempted in patients with ALF and hypotension. Vasopressors are recommended when the mean arterial pressure is < 65 mm Hg in order to maintain a cerebral perfusion pressure of 50 to 80 mm Hg. Norepinephrine is the preferred agent as it has been shown to increase cerebral perfusion in the traumatic brain injury patients.

Epinephrine has been shown to decrease mesenteric blood flow and hence may compromise hepatic blood flow in patients with ALF. Vasopressin is not recommended as it directly causes cerebral vasodilation and may exacerbate intracranial hypertension.

RENAL FAILURE

Acute renal failure is a frequent complication in patients with ALF especially in patients with acetaminophen overdose because of the direct toxic effect of the drug on the kidneys. Aminoglycosides, radiographic dye, and other potentially nephrotoxic agents should be used cautiously. If dialysis is needed, use continuous rather than intermittent modes of renal replacement therapy; continuous venovenous hemodialysis has been shown in randomized trials to result in improved stability in cardiovascular and intracranial parameters when compared with intermittent hemodialysis.

CEREBRAL EDEMA AND INTRACRANIAL HYPERTENSION

Cerebral edema is the single most dangerous early complication of ALF. Patients may have rapid and extreme changes in cerebral perfusion pressure (CPP), especially precipitated by positional changes and movement. At their most severe, acute elevations in intracranial pressure (ICP) may present with seizures, changes in pupillary responses, and decerebrate or decorticate posturing.

Because ICP is subject to rapid changes, ICP monitoring may be used in the management of severely ill patients with ALF. Monitoring ICP serves two purposes: first, it facilitates attempts to reduce ICP and restore CPP whenever ICP rises; second, it enables the caregivers to recognize persistently elevated ICP and reduced CPP, which may cause irreversible brain injury before the patient undergoes liver transplantation. Unfortunately, the specific thresholds that infallibly predict irreversible brain injury are unknown. In the absence of ICP monitoring, frequent evaluation for signs of ICH are needed to identify early evidence of uncal herniation.

The placement of an ICP monitor in a patient with ALF is one of the most contentious issues in managing these patients. No clinical trials demonstrate that ICP monitoring improves clinical outcomes in this disorder (i.e., that the benefits of ICP monitoring outweigh its risks). ICP monitoring is not advised before the patient is transferred to a liver transplant center. Most members of the acute liver failure study group recommend placing an ICP monitor in patients with stage III/IV encephalopathy who are listed for liver transplantation, and those patients not listed in whom intensive medical management offers a reasonable likelihood of recovery (i.e., in patients with acetaminophen-induced ALF). Bleeding diathesis should be corrected prior to placing an ICP monitor. ICP should be maintained below 20 to 25 mm Hg, and the CPP should be maintained above 50 to 60 mm Hg.

In general, patients with intracranial hypertension should be in a quiet environment with limited stimulation, including endotracheal suctioning. Hyperventilation-induced hypocapnia induces cerebral vasoconstriction and decreases ICP. Do not treat spontaneous hyperventilation in ALF, but conversely inducing hyperventilation is not recommended except as emergent rescue therapy in patients with evidence of diencephalic herniation; maintaining a PCO_2 of 25 to 35 mm Hg is reasonable. Dexamethasone or other corticosteroids are of no value in treating increased ICP. Maintenance of euthermia is recommended.

The only treatment of demonstrated therapeutic benefit in the syndrome of elevated ICP in ALF is intravenous mannitol. Administer mannitol, dosed at 0.5 to 1 g/kg, when the ICP is greater than 25 mm Hg for longer than 10 minutes. Assess serum osmolality every 6 hours, and then repeat mannitol boluses if the ICP remains greater than 25 mm Hg and the serum osmolality is less than 320 mOsm/L.

An annotated bibliography can be found at www.expertconsult.com.

Conclusion

Management of ALF requires a team approach and vigilant care by all of the care providers. Transfer patients to a transplant center early in their disease course while it is still safe for transfer, as liver transplantation remains the only curative measure to date for acute liver failure.

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CHAPTER 60

Lower Gastrointestinal Bleeding and Colitis

Stephen Kim ■ Nuzhat A. Ahmad

Lower Gastrointestinal Bleeding (LGIB)

Gastrointestinal bleeding (GIB) is a common clinical problem, accounting for ~1% of acute hospital admissions. Most cases require the intensive care unit (ICU). The ICU management goals of all GIB, upper (UGIB) or lower (LGIB), are stabilization of the patient, prompt diagnosis of the etiology of bleeding, and definitive therapy when possible. This chapter provides an overview for recognizing and treating the most common causes of LGIB.

LGIB is intestinal bleeding that occurs from a source distal to the ligament of Treitz. Various terms to describe LGIB include hematochezia, rectal bleeding, and bright red blood per rectum. These terms fail to indicate the acuity or severity of bleeding, localize the bleeding source, and exclude bleeding from beyond the ligament of Treitz. For example, when all cases of suspected acute LGIB are thoroughly investigated, 10% to 15% are actually bleeding from upper gastrointestinal sources.

Approximately 80% of all patients with acute LGIB cease bleeding spontaneously, but a quarter of these individuals will have recurrent bleeding. The overall mortality of 10% to 15% in LGIB is increased in patients with recurrent or persistent bleeding. In up to 8% to 12% of suspected cases of LGIB, no bleeding source is identified.

HISTORY AND CAUSES

Initial assessment of patients with all GIB should begin with the measurement of vital signs including heart rate and blood pressure (Figure 60.1). Concomitantly with resuscitation, a directed history and a focused physical examination relevant to LGIB should be performed.

The diverse causes of acute LGIB (Table 60.1) can be broadly divided among anatomic, vascular, inflammatory, and neoplastic etiologies. In patients younger than 50 years of age, hemorrhoids are the most common cause, whereas in older patients, diverticulosis and angiodysplasia (arteriovenous malformations) are most frequent. Rectal pain may indicate an anal fissure or hemorrhoids. Abdominal pain may indicate inflammatory bowel disease, ischemia of small or large bowel, or infectious colitis. Painless LGIB, especially in an elderly patient, should increase suspicion of diverticulosis or angiodysplasia. Pain exacerbated with meals can suggest chronic mesenteric ischemia, whereas pain exacerbated by defecation suggests an anal fissure.

The characteristics and color of the patient's stool in acute LGIB also provide clues about the site of bleeding. Blood from the left side of the colon is typically bright red, whereas blood from the right colon is darker and mixed with stool. Blood on the outside of well-formed stool likely represents an anal canal or rectosigmoid lesion such as hemorrhoids or fissures. A change in bowel habits or stool caliber suggests neoplastic causes. If the patient has bloody diarrhea, consider

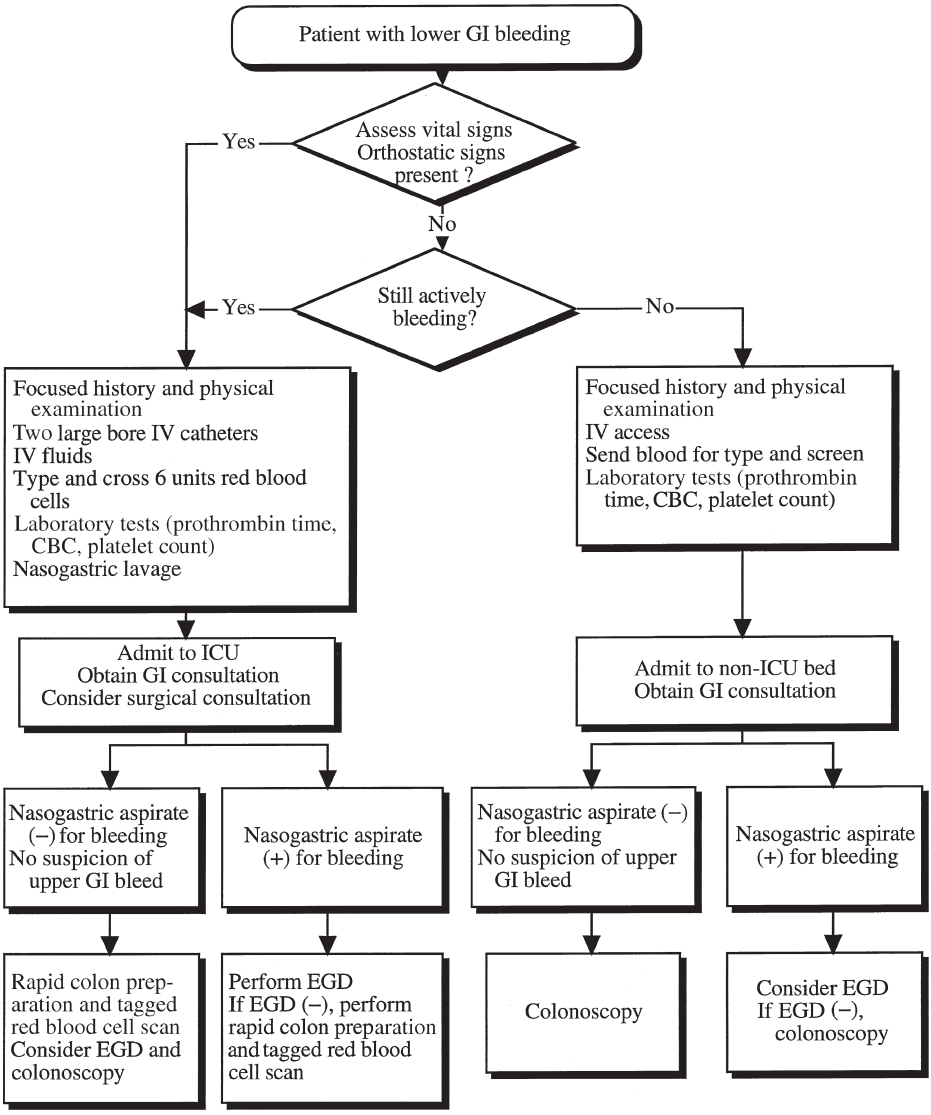


Figure 60.1 Schematic flow diagram of diagnostic evaluation and initial management, including triage, for a patient who presents with a history or signs suggesting lower gastrointestinal bleeding (LGIB) (see text). GI, gastrointestinal; EGD, esophagogastroduodenoscopy; IV, intravenous; CBC, complete blood count; ICU, intensive care unit.

inflammatory bowel disease or infectious colitis. Although hematochezia, the passage of bright red blood or blood clots per rectum, usually indicates an LGIB source, patients with massive UGIB may also present with hematochezia due to rapid transit of blood through the colon. Hematochezia, in combination with hemodynamic instability, should always raise the possibility of a UGIB. Similarly, LGIB from the distal small bowel or proximal colon can present as melena, or black, tarry stools, a finding typically associated with UGIB and thus an absolute diagnosis of the exact site or etiology of bleeding cannot be made based on the color and characteristics of stool.

TABLE 60.1 ■ **Potential Sources for Lower Gastrointestinal Bleeding (LGIB)**

Massive upper gastrointestinal bleeding
Small intestine sources distal to the ligament of Treitz
—Arteriovenous malformation
—Diverticula
—Inflammatory bowel disease
—Meckel's diverticulum
—Neoplasm
—Vasculoenteric fistula (postsurgical)
Large intestine sources
—Arteriovenous malformation
—Colitis (infectious or radiation induced)
—Colonic varices (idiopathic or due to portal hypertension)
—Diverticulosis
—Endometriosis
—Hemorrhoids
—Inflammatory bowel disease
—Intussusception with mucosal compromise
—Ischemia
—Neoplasm
—Solitary rectal ulcer
—Vasculitis

PHYSICAL EXAMINATION

Physical examination may be helpful in determining the cause of LGIB. Pain out of proportion to the physical findings is suspicious for ischemia of the small bowel, colon, or both. In combination with a history of atrial fibrillation, recent myocardial infarction, pressor administration, or systemic hypotension, disproportionate abdominal pain suggests inadequate perfusion of the mesenteric arteries. Stigmata of chronic liver disease may indicate the existence of varices anywhere along the gastrointestinal tract, including the small intestine, colon, and rectum. Rectal examination may reveal a palpable rectal mass or visible fissures.

MANAGEMENT

Patients with LGIB should be admitted to the ICU if they meet appropriate clinical criteria of severity or concomitant disease (Table 60.2). Appropriate resuscitation efforts should be initiated, including large bore intravenous line placements, isotonic intravenous fluid infusions, and red blood cell transfusions. The target hemoglobin level depends on the patient's age and comorbid conditions such as coronary artery disease, emphysema, and chronic kidney disease. For an elderly patient with significant comorbidities, the hemoglobin level should be maintained at 10 g/dL. If a patient has a coagulopathy (International Normalized Ratio [INR] > 1.5) or thrombocytopenia (platelets < 50,000/μL), these should be quickly addressed with transfusions of fresh frozen plasma and platelets, respectively. Vitamin K should be given to patients on warfarin in the setting of active GIB. Early in the management of these patients, a nasogastric lavage should be attempted at bedside to evaluate for a possible UGIB. An upper endoscopy should be considered in patients when a UGIB cannot be definitively excluded based on nasogastric lavage or other clinical information.

TABLE 60.2 ■ **Criteria for Admission to the Intensive Care Unit with Acute Lower Gastrointestinal Bleeding (LGIB)**

Patients Should Be Admitted to the ICU If They Have Any of the Following:
Orthostatic signs* or frank hypotension
Evidence of active hemorrhage
Hemoglobin < 10 g/dL or ≥ 3 g/dL drop from previous baseline
History of previous GI bleeding episode
History of dysfunction of any of the following organ systems
—Cardiac
—Pulmonary
—Hepatic
—Renal

*Orthostatic signs are seen when a change in position from supine to erect causes two or more of the following: (1) pulse increase of 20 beats per minute, (2) systolic blood pressure drop ≥ 20 mm Hg, and (3) diastolic blood pressure drop ≥ 10 mm Hg.
ICU, intensive care unit; GI, gastrointestinal.

This is particularly important in patients with hematochezia and hemodynamic instability. The surgical and interventional radiology services should be consulted if the patient has massive bleeding (requiring more than 6 units of blood) or develops signs of an acute surgical abdomen.

DIAGNOSTIC EVALUATION

Colonoscopy

In general, colonoscopy is the initial examination of choice in the evaluation of suspected LGIB, for the advantages of being both diagnostic and potentially therapeutic. Although cleansing of the colon is usually necessary to allow complete mucosal examination, a colonoscopy can also be performed in an unprepared colon, because blood acts as a cathartic. After adequate preparation of the bowel, the diagnostic accuracy of emergent colonoscopy is high (70% to 92%).

For the purpose of colon cleansing, a balanced electrolyte solution is administered orally or via a nasogastric tube at the rate of 240 mL every 15 minutes. This provides reasonably satisfactory cleansing of the bowel in 4 to 6 hours. Once the rectal effluent becomes clear of stool and blood, colonoscopy is performed. There is no evidence that a rapid bowel purge in the setting of active LGIB will reactivate or increase the rate of bleeding. The only absolute contraindications to colonoscopy in the acute setting are hemodynamic instability or suspicion of a perforated viscus.

Radionuclide Imaging

If the patient continues to bleed but remains hemodynamically stable, a radionuclide scan may help localize the site of hemorrhage. Radionuclide scans can detect bleeding rates as low as 0.05 to 0.1 mL/min. Two types of radionuclide scans are currently available to detect GIB: the technetium (99mTc) sulfur colloid scan and the 99mTc pertechnetate-labeled autologous red blood cell scan. Sulfur colloid has a short half-life and is rapidly cleared from the circulation, so a diagnostic scan requires active bleeding at the time of the scan. In contrast, in patients who undergo the 99 mTc pertechnetate-labeled red cell scan, images are obtained during the first 30 minutes after injection, and then every few hours for up to 24 hours, hence providing further opportunities for identification of intermittent bleeding.

The major disadvantage of radionuclide scans is erroneous localization of the site of bleeding, which can occur in up to 25% of cases. In addition, these tests are purely diagnostic and do not

have the potential for therapeutic intervention. Radionuclide imaging is most helpful in assessing if patients are bleeding vigorously enough to permit visualization of the site by angiography.

Angiography

Angiography can be both a diagnostic and therapeutic intervention. The advantage of angiography is that it does not require a bowel preparation and can accurately localize a bleeding site, thus allowing hemostasis or selective surgical resection. Angiography permits hemostasis with intra-arterial vasopressin infusion or arterial embolization. Instillation of vasopressin should be considered a temporizing maneuver and a bridge to surgical resection, because rebleeding occurs in up to 50% of cases after cessation of the vasopressin infusion. Selective embolization of mesenteric arteries offers a definitive means of controlling the bleeding, but the success rate varies between 44% and 91%.

A significant disadvantage of angiography is that bleeding rates of 0.5 to 1 mL/min are required for localization of the bleeding site. Also, angiography carries a 10% complication rate that includes arterial thrombosis and embolization, renal failure from radiocontrast exposure, and the risk of bowel infarction when attempting embolization. "Superselective" catheterization techniques are currently being employed in an attempt to reduce the infarction risk. Angiography is considered, usually with a therapeutic intent, in patients who have a positive bleeding scan, persistent and recurrent bleeding with a nondiagnostic colonoscopy, or severe bleeding when colonoscopy is not possible.

Computed Tomographic (CT) Angiography

Advances in computed tomography (CT) technology, with shorter scanning times and improved resolution, have led to an increasing role for CT angiography in the initial evaluation of acute GIB. Serial CT scans are performed to localize the source of bleeding. An unenhanced CT is performed first as a baseline image for comparison with later scans. After intravenous injection of a contrast agent, CT angiography can detect GIB when high-attenuation contrast material is visualized within the bowel lumen. Although early experience with multidetector CT angiography has demonstrated promise as a first-line modality for sensitive and accurate diagnosis of acute UGIB, its precise role in the management of LGIB is still evolving.

Small Bowel Investigations

Investigation of the small bowel is warranted in patients in whom a bleeding site is not identified in the colon or upper GI tract. Limited evaluation of the small bowel can be performed with push enteroscopy. When available, wireless video capsule endoscopy should be utilized as the first-line test, which has a high diagnostic yield (up to 60%) for obscure GIB. Capsule endoscopy has the advantage of being a non-invasive test with a low complication rate. The disadvantages are that it does not always provide precise localization of the bleeding site and has no therapeutic potential. Double balloon enteroscopy, an endoscopic technique that allows visualization of the entire gastrointestinal tract, can be used for both diagnostic and therapeutic interventions on the small bowel. However, the procedure is invasive and can take up to 3 hours to complete. The gold standard for evaluating the small bowel is the intraoperative enteroscopy, an invasive test that should only be considered when other diagnostic tests have been exhausted. A specific radionuclide scan to detect a bleeding Meckel's diverticulum may be performed in selected patients at high risk for this disorder, such as adolescents and young adults.

SURGICAL INTERVENTIONS

Surgical therapy for LGIB should be recommended for patients who are exsanguinating from uncontrolled hemorrhage. An emergent endoscopy is indicated in these patients to rule out a

UGIB. A subtotal colectomy is usually performed in patients in whom a bleeding site cannot be localized. Surgery may also be considered in patients with recurrent bleeding despite colonoscopic or angiographic intervention, or both, and in patients with diffuse colonic disease, such as diffuse angiodysplasia, chronic ischemia, or diverticulosis.

Colitis

The discussion of colitis will be limited to the forms of colitis likely to be seen in the ICU. Patients with inflammatory bowel diseases rarely require acute admission to the ICU, and their management will not be considered in this chapter.

CLOSTRIDIUM DIFFICILE COLITIS

Clostridium difficile is a gram-positive, spore-forming anaerobic bacillus that produces two exotoxins, toxin A, an enterotoxin, and toxin B, a cytotoxin, that mediate colitis and diarrhea. *C. difficile* is a common pathogen in hospitalized patients. In this setting, *C. difficile* spores are readily available for transmission, leading to nosocomial outbreaks because they can survive on surfaces for months. The normal human colon resists colonization by *C. difficile* by virtue of its normal endogenous bacteria. However, use of antibiotics can alter this environment so that *C. difficile* may predominate and express toxins. Additional risk factors for developing *C. difficile* infection include advanced age, severe illness, and gastric acid suppression.

Typical clinical features of *C. difficile* infection include watery diarrhea and crampy lower abdominal pain with or without low-grade fever. The symptoms may begin during antibiotic therapy or 5 to 10 days following antibiotic administration. Laboratory evaluation may show an elevated white blood cell count, electrolyte abnormalities consistent with diarrhea-induced volume depletion, and white blood cells in the stool. Flexible sigmoidoscopy, without a bowel preparation, may reveal pseudomembranes. However, the absence of these membranes on sigmoidoscopy does not exclude the diagnosis. Endoscopy is not warranted in patients with classic clinical findings and a positive stool toxin assay.

C. difficile infection is diagnosed using an enzyme immunoassay (EIA), which allows direct detection of *C. difficile* toxin. Cytotoxicity assay (also known as tissue culture assay) is the gold standard for diagnosis of *C. difficile*. However, this test is not performed routinely because of expense and a 48-hour turnaround time.

Worsening abdominal pain and distention, fever, diarrhea, hypovolemia, and marked leukocytosis herald severe or fulminant *C. difficile* infection. Diarrhea usually resolves as the colon dilates and becomes atonic. The diagnosis of *toxic megacolon* is made based on imaging studies that demonstrate the largest colon diameter to be greater than 6 cm. Serial abdominal examinations and radiographs are indicated under these circumstances. Severe localized abdominal pain with signs of peritonitis may represent the development of a perforation. When perforation or severe sepsis develops, a subtotal colectomy with ileostomy is usually necessary.

Metronidazole or vancomycin should be used for the treatment of *C. difficile* colitis (see Chapter 38 for details). If possible, other antibiotics should be discontinued. As a rule, antidiarrheal agents should be avoided. Oral metronidazole or oral vancomycin for 10 to 14 days usually suffices for most cases. In critically ill patients, metronidazole may be given intravenously in addition to oral vancomycin administered via a nasogastric tube. Response to therapy with resolution of diarrhea can be expected in the first 72 hours in more than 95% of patients. However, 10% to 20% of patients will relapse after discontinuation of the therapy. In the ICU setting and in cases of severe infection, patients should be observed diligently for signs and symptoms of fulminant *C. difficile* infection, which mandate an urgent surgical evaluation for a possible colectomy.

TYPHLITIS

Typhlitis is a life-threatening enterocolitis occurring primarily in immunocompromised patients, typically during or following chemotherapy. The exact etiology and pathogenesis are uncertain, with no single pathogenic organism implicated. Gram-positive rods and cocci, gram-negative bacilli and enterococci, and *Candida* have all been identified in the bowel wall. The cecum is almost always affected, and the process often involves the ascending colon and terminal ileum.

Typhlitis should be suspected when a profoundly neutropenic patient (absolute neutrophil count < 500/μL) presents with fever and right lower quadrant abdominal pain. Other symptoms include abdominal distention, nausea, vomiting, and watery or bloody diarrhea. The abdomen may be tender, and the cecum may be palpable as a boggy mass in the right lower quadrant. Abdominal radiograph may reveal a right-sided soft tissue density or an ileus with complete or partial obstruction. Although barium enema may demonstrate nodular mucosa, it is not the test of choice because of the perforation risk. The preferred test is the abdominal CT scan, which demonstrates a thickened, distended, fluid filled cecum, a right lower quadrant soft tissue mass, or cecal pneumatosis. Typhlitis mimics acute appendicitis, and distinguishing between the two is important because of their different management strategies.

Initial treatment is supportive with complete bowel rest, intravenous hydration, broad-spectrum antibiotic administration, and consideration of addition of antifungal agents if the patient fails to improve within 72 hours. The abdominal examination must be followed closely to monitor for the development of peritoneal signs. The surgical service should be alerted if such signs develop or if the patient continues to deteriorate despite intensive medical therapy. Any decision to operate must consider the patient's overall prognosis from the underlying neoplastic disease, as well as some studies demonstrating no improvement in outcome despite surgical intervention. The surgical procedure of choice is a right hemicolectomy with removal of all necrotic debris.

Typhlitis carries a high mortality rate, with overall survival of only 50%. Early recognition and institution of prompt treatment are only speculated to improve morbidity and mortality.

ISCHEMIC COLITIS

Ischemic colitis is caused by a reduction in intestinal blood flow and most commonly arises from occlusive or nonocclusive causes (Table 60.3). Although intestinal ischemia can affect both the small and the large bowel, ischemic colitis is the most frequent form of intestinal ischemia. Most of the affected patients are elderly and develop transient, self-limited ischemia, which resolves without sequelae. A precipitating event is rarely identified. The feared complication of colon ischemia is gangrene, which can be catastrophic if missed.

TABLE 60.3 ■ **Causes of Ischemic Colitis**

Occlusive Causes	Nonocclusive Causes
Abdominal aortic aneurysm	Cardiac dysfunction
Abdominal surgery	Ergotamine
Embolism	Hypovolemia
Thrombosis	Intravenous pressors
Tumor compression	Local hemodynamic disturbances
Vasculitis	Systemic hypotension
	Vasopressin infusion

Patients with acute colonic ischemia typically present with mild abdominal pain. Patients may also develop rectal bleeding or bloody diarrhea within 24 hours after the onset of symptoms. The blood loss is usually mild and does not require transfusions. Physical exam may demonstrate mild tenderness over the affected segment of the colon. In contrast, patients with mesenteric ischemia involving the small bowel appear ill, with abdominal pain that is typically out of proportion to the abdominal exam.

The majority of patients with ischemic colitis will resolve their symptoms with conservative measures, without complications or long-term sequelae. In 10% to 20% of cases, however, patients may develop progressive disease, with increasing abdominal distention and tenderness, worsening ileus, development of necrotic bowel, and ultimately septic shock usually requiring emergent surgical intervention.

Ischemic colitis should be suspected in elderly patients with comorbid conditions such as diabetes, end-stage renal disease on hemodialysis, or peripheral vascular disease who present with lower abdominal pain or rectal bleeding. The differential diagnosis includes infectious colitis, inflammatory bowel disease, diverticulitis, and carcinoma. There are no specific laboratory markers, though leukocytosis (> 20,000/μL) and an anion-gap metabolic acidosis are highly indicative of intestinal ischemia with infarction. Abdominal radiographs and computed tomography scans may demonstrate nonspecific thickening of the affected bowel segment. The definitive diagnosis of ischemic colitis is made based on sigmoidoscopy or colonoscopy findings; and endoscopy should be performed without the delay associated with a bowel preparation. Angiography is indicated when small bowel ischemia cannot be excluded.

Treatment of ischemic colitis is generally supportive with strict bowel rest and intravenous fluids to optimize circulation. Empiric broad-spectrum antibiotics should be instituted in moderate and severe cases. The patient should be monitored for signs of progressive ischemia, which include worsening abdominal pain and distention, fever, leukoytosis, and metabolic acidosis. Colonic infarction requires urgent surgical intervention.

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CHAPTER 61

Upper Gastrointestinal Bleeding

Junsuke Maki ■ Faten N. Aberra

Upper gastrointestinal bleeding (UGIB) is defined as bleeding from a source proximal to the ligament of Treitz (Table 61.1), associated with melena, hematemesis, coffee ground emesis, or aspiration of red blood from a nasogastric tube. *Severe* UGIB results in shock, orthostatic hypotension, decreased hemoglobin concentration (Hgb) by 3 to 4 g/dL, or a transfusion of at least two units of packed red blood cells (pRBCs). Severe UGIB generally necessitates admission to an intensive care unit (ICU) (Box 61.1). Although UGIB occurs more commonly in men, the overall mortality rate of 5% to 10% is similar for both sexes.

Assessment

When a patient presents with gastrointestinal bleeding (GI) bleeding, regardless of the source (upper or lower; see also Chapter 60), the initial management should focus on two main aspects: (1) volume resuscitation with appropriate intravenous (IV) fluids and blood products and (2) identification of the bleeding source, to allow selective therapy. The rapid initial assessment should include determination of vital signs and postural blood pressure changes, a focused history and physical examination, and gastric lavage.

FOCUSED HISTORY

In addition to the presenting symptoms, one should solicit any prior history of GI bleeding, peptic ulcer disease, bleeding diathesis or chronic anticoagulation, renal or liver disease, alcohol abuse, or nonsteroidal anti-inflammatory drug (NSAID) use. It is important to assess the possibility of cirrhosis or other causes of portal hypertension, because management of variceal bleeding remains distinct from that resulting from other UGIB causes. The history may suggest bleeding etiologies. Retching or vomiting episodes immediately preceding the onset of UGIB suggest a Mallory-Weiss tear. A prior abdominal aortic aneurysm repair should prompt consideration of an aortoenteric fistula. Recent instrumentation of the pancreas, liver, or biliary tract should raise the suspicion of hemobilia or hemosuccus pancreaticus. Chronic epistaxis and skin telangiectasias indicate potential hereditary hemorrhagic telangiectasia (HHT, also known as Osler-Weber-Rendu syndrome).

With a clear history of vomiting bright red blood or "coffee grounds" (blood present in the stomach long enough to be acidified by gastric acid turns brown), the localization of UGIB is straightforward. However, occasional bleeding from the posterior pharynx or the lung may be confused with UGIB (see also Chapter 79). Unfortunately, a history of *melena*, resulting from bacterial degradation of hemoglobin, remains nonspecific. Melena commonly arises from brisk UGIB, as well as from a small bowel source (distal of the ligament of Treitz) or a slow bleeding from the right colon.

TABLE 61.1 ■ **Causes of Upper Gastrointestinal Bleeding and Their Frequency**

Cause	Frequency
Erosive gastritis	29.6%
Duodenal ulcer	22.8%
Gastric ulcer	21.9%
Varices (esophageal, gastric)	15.4%
Esophagitis	12.8%
Erosive duodenitis	9.1%
Mallory-Weiss tear	8.0%
Neoplasm	3.7%
Esophageal ulcer	2.2%
Osler-Weber-Rendu syndrome	0.5%
Other	7.3%

From Silverstein FE, Gilbert DA, Tedesco JF, et al: The national ASGE survey on upper gastrointestinal bleeding. I. Study design and baseline data. Gastrointest Endosc 27:73-79, 1981.

BOX 61.1 ■ Indications for Admission to the Intensive Care Unit for Upper Gastrointestinal Bleeding

Active bleeding
Hemodynamically unstable
Known or suspected portal hypertension
Significant comorbid disease
Coagulopathy (e.g., prothrombin time elevated with INR > 2)
Possible sentinel bleed (previous abdominal aortic graft)

INR, international normalized ratio.

FOCUSED PHYSICAL EXAMINATION AND LABORATORY EVALUATION

The physical examination begins with evaluating the patient's hemodynamic status. In addition to directing immediate resuscitation, initial vital signs have prognostic importance: 50% of patients presenting with shock have rebleeding episodes. An orthostatic pulse rise of more than 20 beats per minute implies an acute blood loss of at least 500 mL, whereas an accompanying fall in diastolic pressure of 10 mm Hg or more implies a loss of at least 1000 mL.

The initial examination should survey for stigmata of chronic liver disease (such as spider angiomas, gynecomastia, palmar erythema, ascites, and splenomegaly) or findings suggestive of an underlying malignancy. Cutaneous manifestations of diseases associated with GI bleeding, such as perioral petechiae in HHT, may also be detected.

Initial laboratory evaluation should include a complete blood count (CBC) with a platelet count, coagulation studies (prothrombin time [PT] and partial thromboplastin time [PTT]), and the determination of serum electrolytes, creatinine, blood urea nitrogen (BUN), bilirubin, and liver-associated enzyme levels. The initial blood draw should include a sample to be sent to the blood bank for immediate typing and cross matching.

Intestinal metabolism of blood raises serum BUN so that a BUN:creatinine ratio > 20 (with both BUN and creatinine expressed in mg/dL) supports the diagnosis of UGIB. However, this nonspecific finding can be seen in hypovolemia alone.

BOX 61.2 ■ Initial Management of Patient with Upper Gastrointestinal Bleed in the Intensive Care Unit

Secure two wide-bore intravenous (IV) access lines (preferably two 16-gauge peripheral IV lines or one 16- or 18-gauge peripheral IV line and one central venous catheter)
Give volume replacement, initially with crystalloid
Monitor central venous pressure if patient has underlying cardiac, renal disease, or shock
Send hemoglobin (Hgb) and hematocrit, platelet count, coagulation studies (PT, PTT) stat; follow Hgb frequently
Type and cross-match or type and screen for at least six units of packed red blood cells
For patients in shock with exsanguinating hemorrhage, give unmatched O-negative blood (and other blood products that are available from the blood bank as part of their exsanguination protocol (see Chapter 19 for details) via short 7-8 French rapid infusion catheters (also called *trauma lines*) via a blood warming device with wide-bore stop-cocks and tubing
Insert Foley catheter to monitor urinary output
Obtain abdominal radiograph
Consult gastroenterologist, interventional radiologist, and general surgeon early

PT, prothrombin time; PTT, partial thromboplastin time.

GASTRIC LAVAGE

Even with an obvious history of UGIB, gastric lavage is indicated to clear the stomach in anticipation of endoscopy. Gastric lavage decreases the risk of aspiration for the patient and improves endoscopic visualization. Sometimes, a large-bore tube (e.g., an Ewald tube) unlikely to be occluded by blood clots may be needed. No therapeutic advantage derives from the use of iced saline (versus room temperature tap water or saline) for the lavage fluid. Without evidence of recent bleeding (red blood or coffee grounds) in the initial gastric aspirate, the nasogastric tube may be removed.

A 30% mortality rate has been reported when both the gastric aspirate and stool contain red blood. However, up to 16% of patients with active UGIB may have clear gastric fluid on lavage because of intermittent bleeding or postpyloric bleeding without blood reflux into the stomach. Identification of bile in the gastric aspirate is notoriously inaccurate and is *not* evidence for the absence of UGIB.

Approach to Management

GENERAL CARE

Initial management is individualized based on the patient's hemodynamics, bleeding rate, and comorbidities. General recommendations for the ICU patient start with assuring ample intravenous access (Box 61.2). For hypotensive patients experiencing exsanguination, use short large-bore (7-8 Fr) catheters (often called rapid infusion catheters or trauma lines) in peripheral veins (or longer large-bore catheters in the internal jugular or femoral vein) with corresponding wide-bore tubing and special three-way stopcocks plus a blood warmer. Alternatively, 8 Fr catheter introducer sheaths, routinely used for insertion of pulmonary artery catheters, can also be used (but again without small-bore stopcocks). Initially, give normal saline or Ringer's lactate solution, titrated to keep the heart rate at less than 100 beats per minute and the systolic blood pressure (BP) higher than 100 mm Hg or the mean BP > 60 to 65 mm Hg, if possible. Once available, preferentially replace lost blood volume by transfusing pRBCs. Transfusions remain critical for cirrhotics, who tend to redistribute crystalloids to the extravascular space and acquire massive total body fluid overload. Transfusion timing and

thresholds depend on the patient's hemodynamic stability, underlying conditions, comorbidities, and risk of further bleeding. As a general rule, early consultation with a gastroenterologist and, as appropriate, with an interventional radiologist and general surgeon is recommended for ICU patients with UGIB.

During the first few hours after a bleeding episode, plasma volume and red blood cell mass decrease proportionately, so that the Hgb often remains normal despite significant bleeding. Later, after the plasma volume has expanded from crystalloid therapy, the Hgb may underestimate the quantity of red blood cells present. Transfusion goals can be summarized as (1) pRBCs given to improve oxygen delivery and provide a buffer in case further bleeding occurs, (2) fresh frozen plasma to correct coagulation defects, and (3) platelets to treat thrombocytopenia or platelet dysfunction. Maintaining the Hgb at ~10 g/dL was the traditional target for most patients with UGIBs, but a recent large controlled clinical trial published in 2013 by Villanueva et al indicated that using a threshold of 7 gm/dL was superior to a threshold of 9 gm/dL. In addition, in cases with known portal hypertension and bleeding from gastric or esophageal varices, an Hgb goal of 7 to 8 g/dL adequately resuscitates blood volume without increasing portal pressure and the risk of rebleeding.

Standard ICU monitoring should include continuous electrocardiographic and blood pressure monitoring, the latter either by an arterial catheter or a frequently cycled automated cuff. Patients with a history of congestive heart failure or other significant heart disease should be candidates for central venous or even pulmonary arterial pressure monitoring. Patients with respiratory insufficiency, or altered mental status at increased risk for aspiration, should undergo endotracheal intubation. Similarly, patients with active hematemesis should maintain the left lateral decubitus position to decrease aspiration risk, and tracheal intubation should be considered for airway protection. The importance of frequent repeated clinical assessments of the patient's condition by ICU staff cannot be overemphasized.

ENDOSCOPIC AND ANGIOGRAPHIC INTERVENTIONS

Once the patient is stabilized (and rarely in the unstable patient experiencing exsanguination), urgent endoscopy should be considered. Endoscopy is indicated in resuscitated patients with active hemorrhage, blood product transfusion requirements, persistent hypovolemia, known or suspected portal hypertension, or suspected aortoenteric fistula. Patients who rebleed after initial stabilization should also undergo urgent endoscopy. Endoscopy can be deferred for up to 24 hours in patients with self-limited bleeding and no hemodynamic instability. Esophagogastroduodenoscopy (EGD) correctly identifies the source of bleeding in most cases and also provides valuable prognostic information while allowing the initiation of proper therapy. The accuracy in identifying the bleeding source is highest within the first 12 to 18 hours of hospital admission (approximately 90%) and falls by 30% or more after 24 hours. Accurate identification of endoscopic features can predict the risk of rebleeding (Table 61.2). Because oral radiologic contrast studies offer no therapeutic benefit, and contrast agents may interfere with subsequent endoscopy, they have no role in the initial evaluation of UGIB.

In preparation for upper endoscopy, the patient should have standard ICU monitoring (as noted previously and in Chapter 12), supplemented with respiratory monitoring by continuous pulse oximetry. Equipment for endotracheal intubation should be readily available. A trained endoscopy nurse or ICU nurse must monitor the patient's vital signs and clinical condition during the endoscopy and provide oropharyngeal suctioning. Conscious sedation using an opioid and a benzodiazepine are usually administered with supplemental oxygen. The opioid reversal agent, naloxone, should be readily available. In patients with active bleeding, some gastroenterologists recommend intravenous (IV) erythromycin (250 mg), 20 minutes prior to endoscopy, to promote clearance of retained blood from the stomach and improve visualization.

TABLE 61.2 ■ **Endoscopic Findings in Peptic Ulcers and Their Risk of Rebleeding**

Endoscopic Finding	Risk of Rebleeding
Arterial (pulsatile) bleeding	85%
Nonbleeding visible vessel	40%–50%
Adherent clot	20%–30%
Oozing without visible vessel	20%
Flat blood spot at ulcer base	10%
Clean base	5%

From Silverstein FE, Gilbert DA, Tedesco JF, et al: The national ASGE survey on upper gastrointestinal bleeding. I. Study design and baseline data. Gastrointest Endosc 27:73-79, 1981.

EGD with endoscopic therapy decreases morbidity in acute UGIB. A meta-analysis of 25 prospective trials comparing endoscopic treatment to standard medical therapy for bleeding from peptic ulcers showed statistically significant relative reductions of 69% in the recurrent bleeding rate and 62% in emergent surgeries. When endoscopic diagnosis or therapy is unsuccessful because of obscured visibility or persistent bleeding, angiography comprises an alternative to emergency surgery. Angiography can effectively localize the source of bleeding provided the bleeding is active and the bleeding rate is 0.5 to 1 mL/min or more for angiographic visualization. Angiographic vascular embolization may be effective in patients who fail endoscopic therapy or are poor surgical candidates.

Evaluation and Management of Different Categories of Upper Gastrointestinal Bleeding

GASTRIC AND DUODENAL PEPTIC ULCERS

Ulcer disease occurs in approximately 5% to 10% of the population, and bleeding develops in ~15% of patients with ulcers. The two main causes of ulcers are the use of NSAIDs and infection with *Helicobacter pylori*. Once identified, a gastric or duodenal peptic ulcer may exhibit features that suggest recent or active hemorrhage and that predict the risk of rebleeding (see Table 61.2). Gastric ulcers have a higher overall rebleeding rate than duodenal ulcers. Endoscopic therapies provide benefit only in the presence of high-risk features (arterial bleeding or a visible vessel). Adherent clots should be gently washed; clots washing off easily to reveal active bleeding or a visible vessel warrant therapeutic intervention. Because 80% of all upper GI bleeds stop spontaneously, only lesions predisposed to rebleeding should be treated endoscopically.

In the setting of acute UGIB, gastric acid suppression is essential to decrease the risk of rebleeding and need for surgery. A neutral gastric pH is critical for platelet activation and formation of clots over bleeding vessels. In the past, histamine type 2-receptor antagonists (H_2RA) in conjunction with endoscopic therapy suppressed gastric acid secretion. However, physiologically H_2RA only competitively inhibited histamine receptor activity without suppressing all neural or hormonal signaling cascades. Proton pump inhibitors (PPIs), which competitively inhibit the H+/K+ ATPase, have been proven more effective than H2RAs and therefore serve as first-line therapy for patients with acute UGIB. The typical dosing of IV PPIs is a bolus dose, followed by a continuous infusion for a minimum of 24 hours. For example, a prospective study evaluating IV omeprazole therapy compared to placebo prior to endoscopy showed a significant decrease in length of hospital stay, number of actively bleeding ulcers at endoscopy (6% versus 15%), and subsequent need for endoscopic therapy. In patients with bleeding ulcers and successful initial

hemostasis, IV esomeprazole for 72 hours reduced recurrent bleeding, with sustained benefit for up to 30 days. After endoscopic treatment of clean-based ulcers and those with visible vessels, IV PPI therapy can be switched to oral therapy once the Hgb has remained stable for 24 to 72 hours. However, patients with unstable Hgb despite initial endoscopic therapy can continue IV PPI past 72 hours.

Endoscopic interventions of proven benefit in bleeding peptic ulcers include contact thermal devices, injection with epinephrine, hemoclip application, and argon plasma coagulation. Prospective trials of contact devices used with forceful coaptation of the vessel wall demonstrate decreased rebleeding, shorter hospital stays, less transfusion requirements, and lower hospital costs versus medical therapy alone. Studies suggest that combination therapy with epinephrine injection, followed by a different treatment modality, decreases rebleeding rates compared to injection therapy or thermal coagulation alone. Ultimately, which modality to use depends on the anatomic characteristics of the lesion, the equipment available, and the experience of the endoscopist.

In general, these procedures are considered safe and effective in the proper subset of patients. However, complications from all types of endoscopic therapies occur and include ulceration, induced or worsened bleeding (20%), and perforation (0 to 2%). Bleeding is more common following electrocoagulation and can occur in up to 5% cases, but most often these bleeds can be controlled endoscopically. Repeat hemostasis using thermal coagulation devices within 24 to 48 hours of the initial procedure is associated with up to 4% risk of perforation.

Patients who rebleed after endoscopic therapy usually do so within 48 hours of the initial procedure. In particular, hypovolemic shock on presentation predicts a high risk of recurrent bleeding. Most patients with rebleeding should undergo a repeat attempt at endoscopic therapy. Even without achieving hemostasis, repeat endoscopy can clarify the source of bleeding if transcatheter arteriography or surgery is needed. The timing of either angiography or surgery should be individualized, influenced by transfusion requirements, hemodynamic stability, patient age, and comorbid illnesses. Transcatheter angiography remains a treatment option for refractory UGIB, especially in patients at high risk for surgery, with clinical success seen in roughly 65% of patients. Indications for surgery for refractory bleeding from peptic ulcer disease include hypovolemic shock with recurrent hemorrhage, refractory bleeding despite two endoscopic interventions, and continued bleeding requiring multiple transfusions daily. Rebleeding does not mandate surgery. However, rebleeding from a large posterior duodenal ulcer more likely requires surgery because of the potential risk of penetration into the gastroduodenal artery. Emergency operations for bleeding peptic ulcers have a 10% to 20% mortality risk.

In long-term follow-up studies, the rate of recurrent hemorrhage from peptic ulcer disease was ~33% within the first 1 to 2 years and 40% to 50% after 10 years if healed ulcers were left untreated without chronic acid suppression therapy. This rebleeding rate may be further reduced by eradication of *H. pylori* (when present) and NSAID avoidance. Infection by *H. pylori* should be assessed in all patients with UGIB from peptic ulcers, typically by use of a screening test that may be complemented by biopsies of gastric or duodenal mucosa taken at the time of the EGD.

STRESS ULCER AND GASTRITIS

Bleeding from stress ulcers or severe gastritis occurs commonly in critically ill patients admitted to the ICU for other diagnoses. This bleeding is likely multifactorial, and causes include hypersecretion of acid, altered mucosal defenses, and drug-induced injury. Stress ulcerations typically occur in the fundus or body of the stomach but can arise in the distal stomach and duodenum. They tend to be superficial bleeds arising from the capillary beds. However, deeper ulcerations may also occur, leading to significant hemorrhage or perforation. UGIB can occur in roughly 1.5% to 8.5% of all ICU patients, but the occurrence is as high as 15% in patients not receiving prophylaxis.

BOX 61.3 ■ Indications for Prophylaxis against Stress Ulceration for Patients in the Intensive Care Unit (also see Chapter 12)

Any One of the Following:

Mechanical ventilation for ≥ 48 hours
Coagulopathy
—Platelet count < 50,000
—INR > 1.5
—PTT > 2 × normal control value
History of gastrointestinal (GI) ulceration or bleeding within the last year

Or Any Two of the following:

Sepsis
ICU admission lasting > 1week,
Occult GI bleeding ≥ 6 days
Glucocorticoid therapy (> hydrocortisone 250 mg or equivalent)

From ASHP therapeutic guidelines on stress ulcer prophylaxis. ASHP Commission on Therapeutics and approved by the ASHP Board of Directors on November 14, 1998. Am J Health Syst Pharm 56:347, 1999.

Certain conditions are associated with an increased risk of stress ulcerations and bleeding. All ICU patients at high risk for the development of a stress ulcer should be treated prophylactically (Box 61.3). Although multiple trials have looked at the efficacy of acid suppression at reducing ICU UGIB, methodological flaws or underpowered studies have limited the quality of evidence. In 2013 a large meta-analysis by Alhazzani et al reported that PPI preventive therapy was significantly more effective than H_2RA in preventing clinically important or overt UGIB in ICU patients.

Potentially harmful side effects exist for patients receiving acid suppressive therapy. Some studies suggest an increased risk for nosocomial pneumonias in these patients, possibly because of the migration of bacteria from the duodenum into the stomach, with refluxate traversing up the esophagus into the bronchial tree leading to colonization or pneumonia. Nonetheless, this risk does not outweigh the potential benefit of UGIB prophylaxis in high-risk ICU patients. Finally, hemorrhagic gastritis and stress ulceration may still occur despite such prophylaxis. UGIB developing while a patient is in the ICU should be managed similarly to that for a patient presenting de novo.

ESOPHAGEAL AND GASTRIC VARICES

Increased portal vein resistance, usually a consequence of liver disease, leads to increased flow in portosystemic venous shunts. This may induce the formation of varices in the esophagus and, less commonly, in the stomach. Rarely varices can form more distally in the GI tract. Gastric fundal varices may also arise from splenic vein thrombosis (as a rare complication of acute pancreatitis). Gastroesophageal varices exist in 50% of patients with cirrhosis and correlate with the severity of liver disease. Any varix may spontaneously rupture and result in massive hemorrhage. Variceal bleeding accounts for only 15% of all upper GI bleeding but comprises 30% of severe UGIB. Up to 40% of esophageal variceal bleeds spontaneously resolve, but they still carry a 6-week mortality risk of at least 20%. Compared to other causes of UGIB, variceal bleeding is associated with higher rebleeding rates, transfusion requirements, length of hospitalization, and mortality risk. If no portal pressure lowering procedure is performed, survivors of a first bleeding episode have a 70% risk of a second episode.

Many therapeutic modalities are available for bleeding esophageal varices, including endoscopic, mechanical, pharmacologic, radiologic, and surgical therapies. Endoscopy identifies that bleeding is from nonvariceal sources in up to 50% of patients with known portal hypertension

who present with UGIB. Thus, endoscopy is critical to define the bleeding source and to direct therapy. Identification of active or recent bleeding esophageal varices warrants immediate endoscopic therapy (discussed later). Although initially successful in up to 90% of cases, this therapy has rebleeding rates of 3% to 66%, depending on technique and follow-up regimen.

The two major endoscopic techniques used to stop esophageal variceal bleeding are endoscopic variceal ligation and sclerotherapy. With endoscopic variceal ligation (EVL), tight rubber bands are applied directly onto a varix, thereby strangulating and eventually inducing sloughing of the varix. With sclerotherapy, a sclerosant solution is injected directly into and around a varix to stop bleeding. Although a meta-analysis of 10 randomized controlled trials only showed a trend to more benefit of EVL compared to sclerotherapy, unless contraindicated, band ligation has become the treatment modality of choice.

In patients who fail endoscopic therapy and require stabilization while awaiting radiologic or surgical therapy, temporary use of a tamponading tube (e.g., a Sengstaken-Blakemore or Minnesota tube) is recommended. Both tubes have gastric and esophageal balloons to tamponade the gastroesophageal junction and, if necessary, the esophageal varices themselves. Although they stop the bleeding in over 80% of patients, the tubes have a 10% to 30% rate of major complications, including aspiration, esophageal necrosis and perforation, and tracheal compression. However, the short-term success of this temporizing measure allows stabilization until more definitive treatment can be carried out.

Experience with the proper use of either type of tube is essential to minimize complications. Before trying to insert a tamponading tube, the patient must undergo tracheal intubation for airway protection. Once properly positioned (ideally with the proper position confirmed radiographically), the gastric balloon is inflated with traction applied. Such tamponade of the gastroesophageal junction often suffices to arrest UGIB. If variceal bleeding continues, the esophageal balloon can be inflated. Leaving the balloon(s) inflated for less than 24 hours at a time can prevent pressure necrosis to the esophageal and gastric mucosa. Only the Minnesota tube has an esophageal aspiration port, to monitor for persistent bleeding from esophageal varices. If deploying a Sengstaken-Blakemore tube, attach a nasogastric tube connected to suction proximal to the esophageal balloon before insertion.

Pharmacologic therapy plays a significant adjunctive role in the management of variceal bleeding. Somatostatin and its synthetic analogue, octreotide, reduce portal pressure by indirectly causing splanchnic vasoconstriction and decreased portal inflow, without changing systemic blood pressure or cardiac ischemia. Octreotide significantly reduces transfusion requirements, rebleeding rates, and, in conjunction with endoscopic therapy, may decrease early mortality. In addition, octreotide alone may be as effective as sclerotherapy alone in controlling active hemorrhage. Octreotide is given with an intimal bolus of 50 μg, followed by a continuous intravenous infusion at 50 μg/h for 5 days.

Vasopressin infusions also reduce portal blood flow and pressure and have been used to control hemorrhage in patients with variceal bleeding. However, because of a side effect profile including cardiac, peripheral vascular, and splanchnic ischemia, vasopressin use has been supplanted by octreotide. The synthetic vasopressin analogue *terlipressin* has a prolonged half-life, which allows for intermittent injections as opposed to continuous infusions. Studies show that compared to placebo, terlipressin significantly reduces all cause mortality from variceal hemorrhage. Terlipressin is currently available in Europe, but it has not yet been approved in the United States.

Nonselective beta-blockers provide effective prophylaxis against variceal hemorrhage, but they have no role in the acute management. Beta-blockers should be initiated once active variceal bleeding has stopped and the Hgb remains stable.

In cirrhotic patients with variceal bleeding, multiple complications may occur, including infections in up to 50% of patients. Therefore, prophylactic antibiotic therapy serves as a mainstay to prevent cirrhosis-related complications such as spontaneous bacterial peritonitis. Typically, quinolones or third-generation cephalosporins are used for 7 days.

Approximately 10% to 20% of patients with bleeding varices do not respond to pharmacologic and endoscopic treatment and should be considered for a shunt procedure. A transjugular intrahepatic portosystemic shunt (TIPS) functions similarly to a surgically created portosystemic shunt. A TIPS can rapidly lower portal pressure and achieve immediate control of variceal bleeding, with a success rate for decompression of portal hypertension greater than 90% in selected patient populations.

Variceal bleeding refractory to medical and endoscopic therapy is an accepted indication for TIPS. However, TIPS placement is *contraindicated* in patients with elevated total bilirubin or creatinine levels or with hepatic encephalopathy refractory to medical treatment.

The 1-year survival rate following a TIPS for bleeding varices varies between 48% and 90%, but with a 3% to 4% procedure-related major complication rate and a 1% to 2% associated mortality rate. In addition, 30% of patients will experience a new onset or worsening of hepatic encephalopathy after TIPS. Finally, ~75% of TIPS stenose after 6 to 12 months and require revision by an interventional radiologist. A TIPS often serves as a lifesaving bridge to liver transplantation.

If a TIPS is not available, patients with refractory variceal bleeding should be considered for a surgical shunt. The distal splenorenal shunt is probably the preferred surgical shunt, but ultimately the type of shunt selected depends on the severity of liver disease, presence of ascites, degree of encephalopathy, and experience of the surgeon. An alternative surgical procedure, esophageal transection, may be lifesaving when performed by an experienced surgeon in the acutely exsanguinating patient.

Gastric and small and large bowel varices may also bleed on occasion and are difficult to treat and often rebleed. This bleeding is generally less responsive to the standard therapeutic measures mentioned earlier for esophageal variceal bleeding. In addition, sclerotherapy for gastric varices has been associated with an increased complication rate. Though variceal treatments with tissue adhesives—such as sclerosant, fibrin glue, and cyanoacrylate—have been used outside of the United States with some success, these alternative therapies remain unapproved by the U.S. Food and Drug Administration (FDA). With significant hemorrhage from gastric varices, early consideration should be given to a decompressive shunt procedure.

OTHER CAUSES OF UPPER GASTROINTESTINAL BLEEDING

There are a host of other causes of upper GI bleeding (see Table 61.1).

Erosive gastritis and *duodenitis* are epithelial lesions that do not involve large blood vessels, yet they may still cause significant blood loss. Common causes include NSAID use, alcohol consumption, and physiologic stress. Specific therapy includes avoidance of the offending agent, acid suppression (preferably with the use of omeprazole), and general supportive measures.

Mallory-Weiss lesions are linear tears of the mucosa located at the gastroesophageal junction, usually caused by retching. Although more than 90% of bleeding from Mallory-Weiss tears stops spontaneously, persistent bleeding may be treated with endoscopic therapy.

Vascular anomalies may occur anywhere along the GI tract. Angiodysplasia, arteriovenous malformations, Dieulafoy's lesions, and gastric antral vascular ectasia are reported causes of upper GI bleeding. All are usually amenable to endoscopic therapy.

Aortoenteric fistulas develop in the third part of the duodenum after abdominal aortic aneurysm repair in 0.5% to 2.4% of patients. Their management is surgical, but endoscopy is useful to rule out other causes of bleeding.

Hemobilia presents with the triad of jaundice, GI bleeding, and right upper quadrant pain in 40% of patients. The most common cause is iatrogenic, such as after liver biopsy or percutaneous transhepatic cholangiography. The diagnosis is made by endoscopy (witnessing blood emerging from the major papilla) or angiography. Angiographic or surgical treatment is recommended.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 62

Hemolytic Anemia

Alexander Washington Jr. ■ Marc J. Kahn

The term *hemolysis* was first used in 1901 by William Hunter in his treatise, *Pernicious Anaemia,* when he observed that certain anemias could arise from red cell destruction. This chapter focuses on the causes and treatment of hemolytic anemias.

Clinical Clues to Hemolysis

It is important to identify the clinical clues that indicate red blood cell destruction is taking place. Simply speaking, *hemolysis* can be defined as red cell destruction without evidence of frank blood loss. In general, hemolysis is accompanied by bone marrow compensation for a reduction in red cells. The most obvious example of a marrow response is an elevation in the reticulocyte count, which is generally observed whenever hemolysis is occurring. Other laboratory findings consistent with a diagnosis of hemolysis are an elevation in unconjugated bilirubin, an elevation in the level of lactate dehydrogenase, hemoglobinemia, hemoglobinuria, and a reduction in the serum haptoglobin concentration. These findings are consistent with, but not diagnostic of, hemolysis because these tests have relatively low sensitivity and specificity. As with other hematologic disorders, a review of the peripheral blood smear is essential for making the diagnosis of hemolytic anemia. Findings on the peripheral smear can identify specific pathophysiologic processes (Figure 62.1).

Hemolysis can be divided into two major groups: those that are inherited and those that are acquired (Box 62.1).

Inherited Hemolytic Anemias

Inherited hemolytic anemia may accompany illnesses leading to intensive care unit (ICU) stays, but they are seldom the sole or primary cause for admission to the ICU. The inherited hemolytic anemias can be related to disorders of the erythrocyte membrane, enzymes, globin chain production, and globin chain structure.

RED BLOOD CELL MEMBRANE DISORDERS

Disorders of the erythrocyte membrane are thought to cause hemolysis by shortened red blood cell survival and splenic destruction. These disorders include hereditary spherocytosis, hereditary elliptocytosis, hereditary pyropoikilocytosis, and hereditary stomatocytosis. These disorders are due to mutations in erythrocyte membrane support proteins such as ankyrin, spectrin, protein 4.1, and others. They are characterized by lifelong red blood cell destruction and varied levels of anemia. Some of these disorders are associated with splenic dysfunction and they may predispose patients to infections with encapsulated organisms such as pneumococcus, hemophilus, or meningococcus.

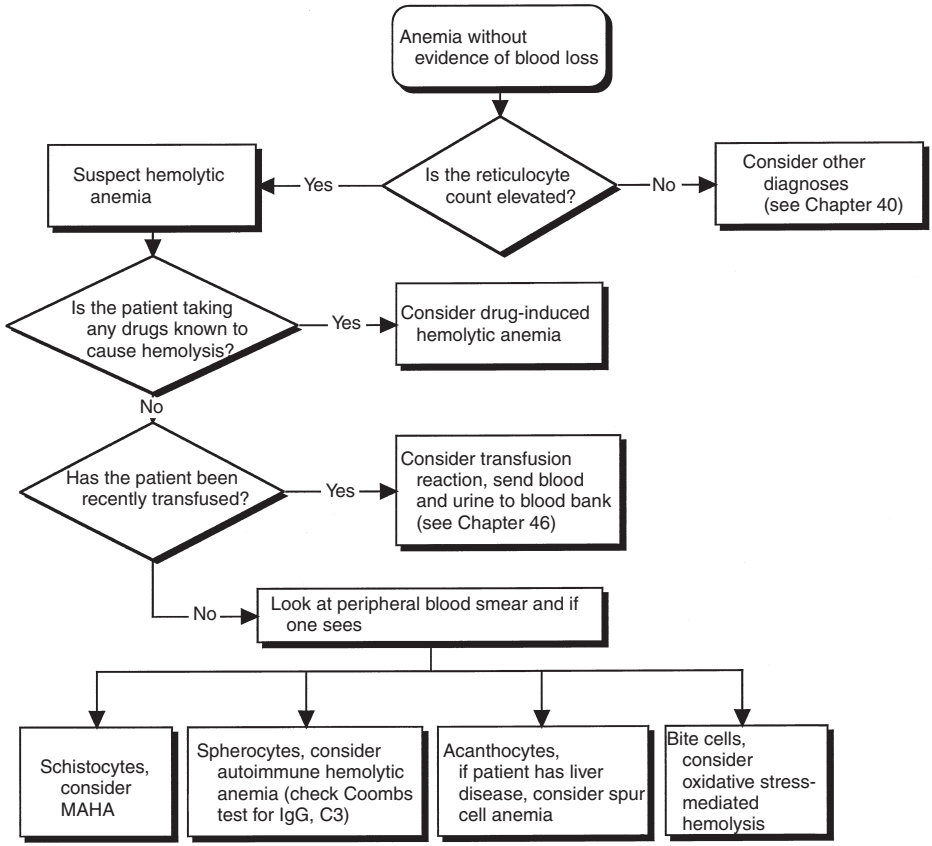


Figure 62.1 Schematic flow diagram of diagnostic workup of suspected acquired hemolytic anemia. MAHA, microangiopathic hemolytic anemia.

RED BLOOD CELL ENZYME DISORDERS

Disorders of erythrocyte enzymes can lead to hemolytic episodes. These enzyme defects include deficiencies of enzymes used on the glycolytic pathway such as pyruvate kinase (PK) deficiency (also called *nonspherocytic hemolytic anemia*). PK deficiency usually presents in children with unexplained anemia. The most important enzyme defect for ICU patients is glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD is an enzyme that generates nicotinamide-adenine dinucleotide phosphate, which, in turn, is used by erythrocytes and other cells as an antioxidant.

G6PD deficiency has its highest prevalence among Kurdish Jews, with an estimated prevalence of more than 60%. G6PD deficiency is also found in malaria-rich regions of the world such as Africa. As the gene coding for G6PD is on the X chromosome, males are preferentially affected. G6PD-deficient individuals, as a rule, do not have significant hemolysis unless subjected to oxidant stress, which is usually caused by drugs or fever. Hemolysis is most often secondary to exposure to oxidant drugs, such as quinine, phenazopyridine, or dapsone. A more complete list of medications to be avoided in G6PD-deficient patients can be found in Box 62.2.

Diagnosis of G6PD deficiency can be made by review of the peripheral smear that may show red blood cell blistering or Heinz bodies (inclusions of denatured hemoglobin seen in smears

BOX 62.1 ■ Differential Diagnosis of Hemolytic Anemia

Inherited Hemolytic Anemias

Membrane defects (spherocytosis, elliptocytosis, pyropoikilocytosis, stomatocytosis)
Enzyme defects (Embden-Meyerhof pathway defects, hexose monophosphate shunt defects, nucleotide enzyme defects)
Thalassemias
Hemoglobinopathies

Acquired Hemolytic Anemias

Immune hemolysis
- Autoimmune
  - Paroxysmal cold hemoglobinuria
  - Warm antibody hemolytic anemia
  - Cold agglutinin disease
- Alloimmune
- Drug-induced

Microangiopathic hemolytic anemia (MAHA)
Infection-related hemolysis
Spur cell anemia

BOX 62.2 ■ Medications to Be Avoided in Persons with Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

Acetanilid	Nitrofurantoin	Sulfamethoxazole
Dapsone	Phenazopyridine	Sulfanilamide
Methylene blue	Primaquine	Sulfapyridine
Nalidixic acid	Sulfacetamide	Toluidine blue
Niridazole	Quinine	

stained with methylene blue). Laboratory analysis of G6PD levels and phenotype should be performed at times other than acute hemolytic episodes because the cells that remain after a hemolytic episode tend to be those with higher levels of G6PD. Proper treatment of this disorder is avoidance of exposure to these oxidant drugs. Once hemolysis occurs, it tends to be self-limited and the care of patients remains supportive, including judicious use of red cell transfusions only when hemolysis is of crisis proportion.

GLOBIN CHAIN PRODUCTION AND STRUCTURE DISORDERS

Disorders of globin chain production and structure include the thalassemias and hemoglobinopathies, such as hemoglobin S and hemoglobin C. These mutations cause unstable hemoglobins, which shorten red blood cell survival. Of relevance to ICU care, patients with sickle cell anemia can develop acute chest syndrome characterized by shortness of breath, chest pain, hypoxia, fever, and an infiltrate on chest radiograph. These patients may become critically ill and may require mechanical ventilation. Acute chest syndrome may be secondary to in situ thrombosis, pneumonia, or fat embolism. Regardless of etiology, patients with acute chest syndrome require red cell replacement either through simple transfusion or exchange transfusion. Red cell replacement is associated with improvement in morbidity and mortality. When exchange transfusions are required, the goal is a hemoglobin of 10 g/dL with 30% sickled cells.

TABLE 62.1 ■ **Treatment of Acquired Hemolytic Anemias**

Disorder	Treatment
Paroxysmal cold hemoglobinuria	Usually self-limited; can treat underlying disease
Warm antibody	Prednisone; may also need danazol, IgG, or splenectomy; rituximab (rituxan) for patients refractory to steroids; immune globulin and splenectomy
Cold agglutinin disease	Keep patient warm; prednisone not helpful
Drug induced	Remove offending agent
Acute hemolytic reaction	Immediately stop transfusion; support blood pressure, control bleeding, and maintain urine output
Microangiopathic hemolytic anemia	Treat underlying condition; avoid giving platelets
Infectious causes	Treat underlying infection
Spur cell anemia	Supportive care
Paroxysmal nocturnal hemoglobinuria (PNH)	Usually supportive (blood transfusion, anticoagulation) eculizumab (Soliris) in select patients

Acquired Hemolytic Anemia

Acquired hemolytic anemias can be severe and can result in ICU admission (Table 62.1).

Autoimmune Hemolytic Anemias

Autoimmune hemolytic anemias (AHAs) result from the destruction of red blood cells when antibodies recognize antigens on their surfaces. There are three types of autoimmune hemolytic anemias: (1) paroxysmal cold hemoglobinuria, (2) warm antibody autoimmune hemolytic anemia, and (3) cold agglutinin disease.

PAROXYSMAL COLD HEMOGLOBINURIA

Paroxysmal cold hemoglobinuria is exceedingly rare and is characterized by both recurrent episodes of massive hemolysis after exposure to cold and the presence of the Donath-Landsteiner antibody (an antibody to the P antigen on red blood cells). This IgG antibody binds to the erythrocyte in the cold and causes complement-mediated hemolysis on warming. It is classically associated with congenital or tertiary syphilis. Therapy has been supportive, with complete remission on treatment of the infection. With the advent of effective therapy for syphilis in modern times, paroxysmal cold hemoglobinuria is more often seen in children after a viral infection. It is usually a single episode without recurrences. Clinical features include aching pains in the back and legs, abdominal pain, fevers, and chills followed by hemoglobinuria and occasional jaundice. This condition is usually self-limited and does not require specific therapy.

WARM ANTIBODY AUTOIMMUNE HEMOLYTIC ANEMIA

Common autoimmune hemolytic anemias are divided into warm antibody–induced hemolytic anemia and cold antibody–induced hemolytic anemia (also called *cold agglutinin disease*). The temperature classification is derived from the temperature at which red blood cell destruction occurs—37.0° C in the case of warm hemolytic anemia and temperatures lower than normal body temperature in the case of cold agglutinin disease.

Warm antibody–induced hemolytic anemia occurs when antibodies of the IgG class bind to Rh-type or other antigens on the erythrocyte surface at body temperature. Hemolysis is usually the result of the splenic macrophage destruction of erythrocytes. Macrophages, in the Billroth cords of the spleen, recognize the Fc portion of the antibody bound to the erythrocyte via their Fc receptors. The Kupffer cells in the liver may also recognize antibody-coated cells, but this is less common. On recognition and binding by macrophages, partial phagocytosis results in the red blood cells becoming spherocytes. They are subsequently ingested by macrophages. Complement-mediated erythrocyte destruction is rare in warm antibody-induced hemolytic anemia.

Warm hemolytic anemia can be primary, that is, occurring without underlying disease, or secondary, such as that resulting from lymphoproliferative disorders (typically chronic lymphocytic leukemia or lymphoma). This condition is also associated with connective tissue disorders such as systemic lupus erythematosus, other neoplasms such as ovarian carcinoma, chronic inflammatory diseases such as ulcerative colitis, and ingestion of drugs such as alpha-methyldopa.

The presenting complaints of individuals with warm antibody autoimmune hemolytic anemia (AHA) are usually secondary to anemia and include decreased exercise tolerance, shortness of breath, or angina. Additionally, patients present with jaundice, fever, or hepatosplenomegaly.

Review of the peripheral smear is essential in making a diagnosis of warm antibody AHA. Because of partial ingestion of erythrocytes by splenic macrophages, the cells assume a spherocytic shape to provide volume for a decreased surface area. Spherocytes on the peripheral smear are therefore the hallmark of warm antibody AHA. The peripheral smear may also show polychromasia and an elevated reticulocyte count. Diagnosis of warm antibody AHA requires a positive direct Coombs test to demonstrate the presence of immunoglobulin, complement, or both on the surface of the patient's erythrocytes. These patients also may have free antibody in their serum, which would also result in a positive indirect Coombs test.

Transfusing patients with warm antibody AHA is problematic for two reasons. First, it is often difficult to crossmatch these individuals because of the presence of a panreactive antibody in their serum. Second, the transfused cells have a short half-life because of the hemolytic process. Therefore, transfusion should be avoided in all but the most serious conditions in which immediate increase in the oxygen-carrying capacity of the blood is needed. Even then, the least incompatible blood should be transfused slowly and care taken to follow the hematocrit/hemoglobin because the transfused blood is not likely to sustain the increased level for a long period of time.

Treatment of warm antibody AHA involves preventing macrophage recognition and destruction of the antibody-coated cells. The traditional treatment is glucocorticoid administration. Glucocorticoids appear to work by decreasing macrophage recognition of antibody-coated cells as well as decreasing production of the autoantibody. Patients are treated with oral prednisone at a dose of 1 to 2 mg/kg daily. Alternatively, the equivalent daily dose of intravenous methylprednisolone may be used. High-dose glucocorticoid therapy is continued for 10 to 14 days, at which point the prednisone is tapered. Approximately two thirds of patients with warm antibody AHA respond to prednisone, and 20% have a complete remission.

The immunosuppressant rituximab (an anti-CD-20 monoclonal antibody used primarily to treat B-cell non-Hodgkin lymphoma) has been found safe and effective in some patients refractory to steroids. Rituximab works by decreasing antibody production through the destruction of B lymphocytes. Both intravenous immune globulin (IVIG) and splenectomy have also been used in the treatment of warm antibody–induced AHA. Splenectomy works by removing the site of erythrocyte destruction. However, splenectomy is effective in only about two thirds of patients. Alternatively, immunosuppressive agents such as cyclophosphamide or azathioprine, the nonvirilizing androgen danazol, and the purine analogue 2-chlordeoxyadenosine have been used with varied success. The overall prognosis for warm antibody AHA is variable, with frequent relapses common.

COLD AGGLUTININ DISEASE

Cold agglutinin disease is characterized by the presence of monoclonal antibodies of the IgM class that react with erythrocytes at temperatures less than body temperature, usually between 28.0° and 31.0° C. The target antigen on the erythrocyte is usually an oligosaccharide of the I/i system that is a precursor to the ABH and Lewis blood group antigens. As IgM can readily fix complement, a patient's red blood cells become coated with complement. This results in cell injury by direct lysis and hepatic macrophage and splenic macrophage opsonization. Usually, the progression of the complement cascade is halted at the formation of C3b because of protective proteins on the red blood cell surface.

Cold agglutinin disease may be a primary disorder but is more often associated with infections, such as *Mycoplasma* pneumonia or mononucleosis, or with preexisting B-cell neoplasms. The clinical presentation of patients with cold agglutinin disease is usually a chronic hemolytic anemia with or without jaundice. The peripheral smear may show spherocytosis that is much less pronounced than in the case of warm antibody AHA. In addition, autoagglutination is typically seen on the peripheral smear. Cold agglutinin disease can be confirmed by the presence of complement (C3b) on the red blood cell surface by a positive direct Coombs test for complement. Because IgM readily dissociates from the erythrocyte, it usually is not detected on the cell surface.

The treatment of patients with cold agglutinin disease is supportive. Patients must be kept warm, particularly their extremities. Glucocorticoids, danazol, immunoglobulin, and splenectomy are, as a rule, not beneficial. As in warm antibody–induced AHA, rituximab has been effective in selected patients with cold agglutinin disease. In severe anemia, red blood cell transfusions can be given but must be warmed before use. Likewise, intravenous fluids must be warmed before infusion to prevent antibody from attaching to erythrocyte membranes. Although the primary form of the disease is usually chronic with a benign course, the postinfectious forms are generally self-limited.

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired red cell membrane disorder associated with abnormal activation of the complement system and resultant hemolysis. Patients with PNH, in addition to increased risk of hemolysis, have increased risk of thrombosis, often in unusual sites such as mesenteric, hepatic, and portal veins. A monoclonal antibody, eculizumab (Soliris), has been developed that targets the disordered complement system, reduces hemolysis, and, in conjunction with anticoagulant therapy such as warfarin, has improved outcomes in PNH patients.

Drug-Induced Hemolytic Anemia

Since the first description of drug-induced hemolytic anemia by the drug Sedormid in 1949, the list of drugs associated with hemolytic anemia has grown steadily. Drugs can cause hemolytic anemia by several well-described mechanisms. The first mechanism is via a hapten process. *Penicillin* is the prototype of this process. Penicillin, when given in high doses, can become bound to the red blood cell membrane. IgG antibodies are then produced to this complex, causing red blood cell destruction by splenic macrophages. In the case of *quinidine*, red blood cells are destroyed when drug-antidrug complexes become bound to the red blood cell membrane. This has also been called an *innocent bystander reaction. Alpha-methyldopa* is able to induce the formation of antibodies, usually IgG, against red blood cell antigens. The clinical presentation of drug-induced hemolytic anemia is similar to that for autoimmune hemolytic anemias. Hemolysis tends to be mild, and the only treatment needed in most circumstances is discontinuation of the offending drug.

Acute Hemolytic Transfusion Reactions

The major source of mortality from blood transfusion involves the transfusion of allogeneic incompatible blood (see also Chapter 46). The overwhelming majority of these mishaps are due to clerical error in which properly crossmatched blood is given to the wrong patient. After the infusion of alloincompatible blood, the patient usually experiences fever, low back pain, chest pain, hypotension, nausea, and vomiting. Shock may soon follow and lead to multiorgan failure; hemoglobinuria can also contribute to the development of acute renal failure. A consumptive coagulopathy develops in up to one third of patients.

The hemolytic process is due to the intravascular destruction of red cells by complement as well as to hepatic and splenic clearance of the incompatible erythrocytes. Laboratory findings include the presence of hemoglobinemia (which can be detected at the bedside by pink staining of the patient's plasma when held up to a light) and hemoglobinuria. Demonstration that the blood recipient's plasma agglutinates the transfused red blood cells is also evidence for a major transfusion reaction.

The initial critical management of patients suffering acute hemolytic transfusion reactions is the immediate cessation of the transfused blood product. That product as well as samples of patient's blood and urine should be sent to the transfusion service (blood bank) for analysis. Bleeding is a major complication of an acute hemolytic reaction and is usually caused by a consumptive coagulopathy. Some authors suggest that heparin may be helpful in this instance. When used, heparin is usually given at several hundred units an hour at a constant infusion without a bolus. It is also important to maintain the fibrinogen level at greater than 100 mg/dL in patients with acute hemolytic reactions. This is best accomplished with cryoprecipitate. To protect the kidneys from the toxic insult, the systolic blood pressure should be maintained at greater than 100 mm Hg by the use of fluids, blood products, and vasopressors, if necessary. Although the use of mannitol is controversial, maintaining a urine output of at least 100 mL/h for the first 24 hours is important to preserve renal function. This can be carried out by giving loop diuretics (e.g., furosemide) or mannitol and intravenous hydration.

Microangiopathic Hemolytic Anemia

Microangiopathic hemolytic anemia (MAHA) occurs when fibrin strands deposited in the microcirculation shear circulating erythrocytes. This results in fragmentation of red blood cells. As fibrin is usually deposited by thrombotic processes, patients with MAHA are frequently thrombocytopenic. MAHA is felt to be primary in the case of thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). In these conditions (see Chapter 63), MAHA is accompanied by fever and microthrombosis of small vessels in the kidney, central nervous system, or both. Most cases of TTP have a deficiency in a metalloproteinase, ADAMTS 13, which normally cleaves and degrades ultra-large von-Willebrand factor multimers (ULvWF) released from injured endothelial cells. Undegraded multimers cause platelet activation and aggregation and microthrombi leading to red cell fragmentation and thrombocytopenia. Other conditions that predispose to MAHA include malignant hypertension, eclampsia, stem cell transplantation and organ rejection, cancer, collagen vascular disorders, congenital arteriovenous malformations, and drugs such as cyclosporine A, mitomycin C, ticlopidine (Ticlid), and clopidogrel (Plavix). Clopidogrel is a less common cause of TTP than ticlopidine and has largely replaced the latter in stroke prevention and thrombosis prophylaxis following vascular procedures.

The clinical features of MAHA relate to the underlying disease causing the process. Common findings include anemia, thrombocytopenia, renal dysfunction, fever, and central nervous system abnormalities. The peripheral smear is diagnostic of this condition. Classic features include the presence of fragmented red blood cells, schistocytes (see Figure 63.1 in Chapter 63), decreased

platelets, and nucleated red blood cells. High levels of lactate dehydrogenase occur and can be used to follow the course of the disease.

Treatment of MAHA is usually directed toward treating the underlying disorder. In the case of TTP or hemolytic uremic syndrome (HUS), plasmapheresis has greatly altered the natural history, causing resolution in more than 80% of patients. Plasmapheresis should be prompt, immediately following diagnosis. Although red blood cells can be used to treat the underlying anemia in cases of MAHA, they should be washed to prevent the accidental infusion of platelets or platelet particles. Platelet transfusions should be avoided in the case of TTP because their use may cause sudden death attributed to acute microthrombosis in vital organs.

Other Hemolytic Conditions

A variety of infectious organisms can cause hemolytic episodes through a variety of mechanisms. First, organisms can invade the erythrocyte directly, as is the case with *malaria, babesiosis,* and *bartonellosis*. Alternatively, the organism can elaborate a hemolytic toxin such as *Clostridium perfringens*. In both circumstances, treatment is supportive, with therapy directed against the infecting organism.

Patients with advanced liver disease caused by alcohol and cirrhosis can rarely acquire a rapidly progressive hemolytic anemia characterized by acanthocytes (spur cells) on the peripheral smear. This condition is usually accompanied by jaundice and splenomegaly. It is usually progressive, with death occurring in weeks to months.

An annotated bibliography can be found at www.expertconsult.com.

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This is a review of mechanisms underlying thrombotic complications of PNH.

CHAPTER 63

Idiopathic and Thrombotic Thrombocytopenias

Marcelo Blaya ■ Marc J. Kahn

Moderate to severe thrombocytopenia is a major feature of several disorders that accompany or lead to stays in the intensive care unit (ICU). Immune (idiopathic) thrombocytopenic purpura (ITP) and thrombotic thrombocytopenic purpura (TTP) are two such conditions. Early and accurate diagnosis and rapid application of appropriate therapy are keys to the successful management of patients with these disorders. Accurate diagnosis requires differentiating the thrombocytopenia of ITP and TTP from each other as well as from other thrombocytopenic conditions. The diagnostic workup should begin with a carefully focused history and physical examination, followed by an examination of the peripheral blood smear (Figure 63.1). Blood products should *not* be given to a nonbleeding patient with thrombocytopenia until the smear is inspected, particularly to evaluate for the presence or absence of schistocytes and rule out the presence of TTP. Moreover, during the initial evaluation, patients should be safeguarded from iatrogenic bleeding complications resulting from a low platelet count (Box 63.1).

Immune Thrombocytopenic Purpura

MECHANISM AND DIAGNOSIS

Autoantibodies directed against the patient's platelets cause ITP. These antibodies are usually directed against the platelet glycoproteins Ib/IX or IIb/IIIa, and their binding results in platelets being destroyed in the spleen. Destruction occurs by splenic macrophage Fc-receptor recognition of antibody-coated platelets. An additional contributing factor to thrombocytopenia observed in ITP is decreased platelet production. Patients with ITP usually have mucosal bleeding, severe anemia, or incidental thrombocytopenia on routine blood counts. Fortunately, severe bleeding such as intracranial hemorrhage is rare in ITP.

ITP is characterized by a decrease in the number of platelets seen in the peripheral smear. Occasionally, large platelets can be found. Erythrocytes and leukocytes should appear normal. Bone marrow examination may show an increased number of megakaryocytes, indicating an appropriate response to the increased platelet destruction. Platelet antibody testing is usually unhelpful because of low sensitivity and specificity.

ITP remains a diagnosis of exclusion after other causes of thrombocytopenia are ruled out. Box 63.2 lists the differential diagnosis of thrombocytopenia without microangiopathy. Evans syndrome is also an antibody-mediated disease, with antibodies directed against both platelets and erythrocytes. The destruction of erythrocytes occurs with the same mechanism as does the destruction of platelets. Bone marrow aspiration is an appropriate test to establish the diagnosis in patients older than 60 or in those considering splenectomy.

ITP has been associated with other conditions in up to 20% of cases. In this setting, it is often called secondary ITP. Causes of secondary ITP include collagen vascular diseases,

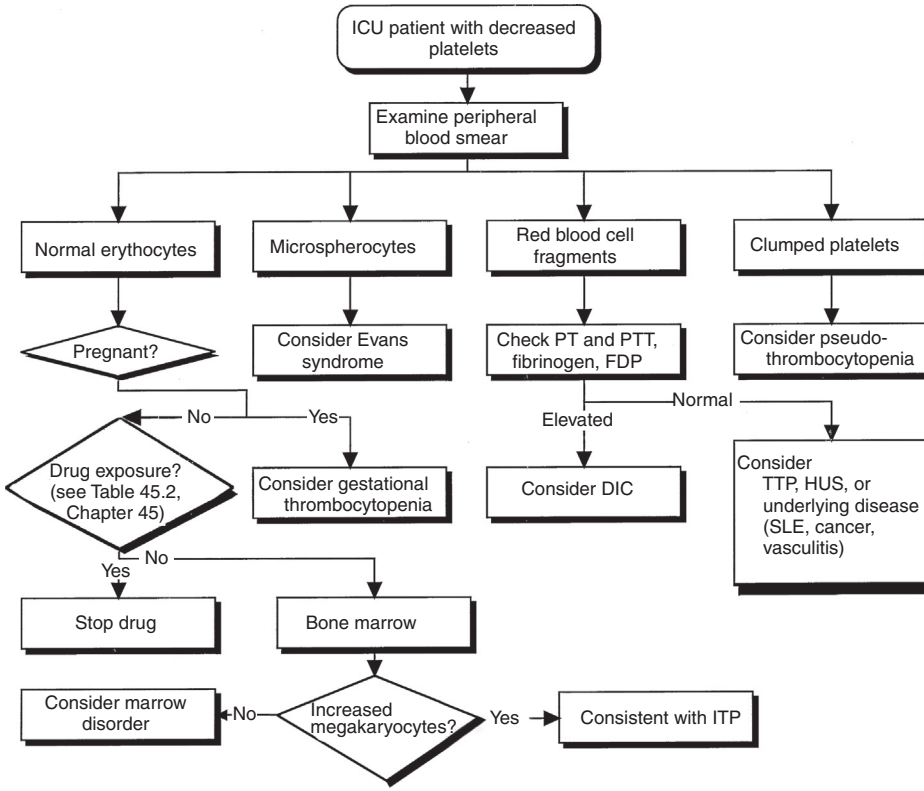


Figure 63.1 Schematic diagram to evaluate an ICU patient with thrombocytopenia. PT, prothrombin time; PTT, partial thromboplastin time; FDP, fibrin degradation products; DIC, disseminated intravascular coagulation; TTP, thrombocytic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; SLE, systemic lupus erythematosus; ITP, idiopathic thrombocytopenic purpura.

BOX 63.1 ■ Safeguards for Patients in the Intensive Care Unit with Thrombocytopenia from Any Cause

No antiplatelet drugs that interfere with platelet function (aspirin, NSAIDs, high doses of penicillin, or semisynthetic penicillins)
No intramuscular injections
All blood draws need direct pressure and pressure dressings
After removing central venous catheters or arterial lines, one must exert direct pressure over the site for a minimum of 10 minutes followed by a pressure dressing
Flush lines with normal saline and avoid heparin unless absolutely necessary
Avoid indwelling bladder catheters, rectal tubes, nasotracheal and nasogastric tubes
Evaluate for other coagulopathies and obtain hematologic consultation if the need for anticoagulation is anticipated

NSAIDs, nonsteroidal anti-inflammatory drugs.

BOX 63.2 ■ Differential Diagnosis of Thrombocytopenia without Microangiopathy*

ITP
Evans syndrome
Incidental gestational thrombocytopenia
Bone marrow failure
Alcohol
Drug-induced thrombocytopenia
Systemic lupus erythematosus

*Microangiopathy denotes the presence of schistocytes (fragmented red blood cells) on peripheral smear. ITP, immune thrombocytopenic purpura.

lymphoproliferative disorders, infections, and other autoimmune syndromes. Thrombocytopenia is also a common manifestation of human immunodeficiency virus (HIV) disease, presumably caused by increased platelet destruction on an immune basis. The clinical features of HIV-associated ITP are similar to those of idiopathic ITP. However, ITP associated with HIV infection in patients with hemophilia is of particular concern because these patients are at much higher risk for catastrophic bleeding than are patients with primary ITP.

TREATMENT

There are few well-controlled clinical studies on which to base recommendations for treatment of adult patients with ITP. Most of the literature on the treatment of ITP consists of case series without a control group. Treatment of ITP depends on the platelet count and clinical presentation. Spontaneous bleeding in ITP is rare with platelet counts > 50,000/μL. This number of platelets is also sufficient for most surgical procedures. Although rare, spontaneous bleeding has been reported in ITP patients with platelet counts in the 30,000 to 50,000/μL range. Because as many as 5% of adults and 40% of children with ITP have spontaneous remissions, it is safe to observe patients with ITP and platelet counts > 30,000/μL if they are not actively bleeding.

Actively bleeding patients with ITP require urgent management. Platelet transfusions are usually ineffective because of shortened platelet survival despite platelet counts increasing transiently in some patients. Pretreatment with intravenous immunoglobulin (IVIG) at a dose of 0.4 to 1.0 g/kg may increase the life span of the transfused platelets and cause an increase in the platelet count several days later by modulating the immune response. This therapeutic modality is expensive, costing between $5000 and $10,000 per treatment course. Antifibrinolytic agents such as epsilon-aminocaproic acid can effectively reduce hemorrhage, but the use of these agents is complicated by an increased incidence of thrombosis.

Glucocorticoids have become the mainstay of treatment for ITP that is symptomatic or when the platelet count falls to < 30,000/μL. The typical daily dose of prednisone is 1 mg/kg. This inexpensive treatment elevates platelet counts in about two thirds of treated patients. Most patients exhibit a decline in platelet count when the prednisone dose is tapered and therefore require additional therapy. The anti-CD20 monoclonal antibody, rituximab, has shown efficacy in patients who relapse following glucocorticoid therapy. Rituximab is typically given by monthly intravenous infusions of 375 mg/m^2 for four doses. Alternatively, anti-D immune globulin has shown efficacy in patients with ITP who are Rh positive and have an intact spleen. Splenectomy can produce sustained increases in platelet counts in more than two thirds of patients with ITP. Pneumococcal, meningococcal, and hemophilus vaccines should be given 2 weeks before splenectomy to reduce the risk

of severe complications resulting from postsplenectomy pneumococcal bacteremias. Some patients have a relapse of ITP months or even years after splenectomy. This is attributable to the presence of an accessory spleen. These spleens occur in up to 20% of patients and are easily detected by radionuclide scanning. After the removal of accessory spleens, ITP resolves in many of these patients.

ITP may become refractory to conventional therapy in some patients. There is no evidence and very little consensus about how to treat patients who do not respond or who respond transiently or incompletely to initial therapy with glucocorticoids. Modalities of therapy for refractory ITP include the use of immunosuppressive agents, such as azathioprine, cyclophosphamide, or vinca alkaloids. Alternatively, danazol, an androgenic steroid, can be useful for sustaining partial remissions or a decrease the glucocorticoid dose. Small case series report that combination chemotherapy and high-dose dexamethasone is efficacious in the management of chronic refractory ITP.

As mentioned previously, the monoclonal antibody against CD-20, rituximab, has been used in patients with refractory ITP, either before or after splenectomy. Again, most of the data here derive from case series and systematic reviews. The majority of these studies had a relatively short follow-up time, and based on this evidence, rituximab was suggested to be not as effective as splenectomy for establishing durable complete responses, nor was it safer than splenectomy.

Immune Thrombocytopenic Purpura in Patients with Human Immunodeficiency Virus or in Pregnancy

Pregnancy and HIV infection are two special circumstances associated with ITP. Although HIV-infected patients are clinically similar to other patients with ITP, they manifest dramatic elevations in platelet counts when they receive zidovudine therapy. Presumably, the antiretroviral agents inhibit virally mediated ITP.

Pregnancy can lead to thrombocytopenia from a variety of causes, including thrombocytopenia of pregnancy, ITP, and preeclampsia and eclampsia (Chapter 72). The management of ITP early in pregnancy is similar to the management of ITP in nonpregnant patients except that splenectomy is typically contraindicated. Exceptions include refractory cases in the second trimester or a bleeding patient who has failed glucocorticoids and IVIG. In pregnancy, treatment is required for women with platelet counts of < 10,000/μL and for those with platelet counts of 10,000 to 30,000/μL who are in their second or third trimester and bleeding. The critical management decision in ITP during pregnancy focuses on delivery of the fetus. Although rare, infants born to women with ITP may be thrombocytopenic. As a precaution, many obstetricians recommend prednisone therapy for the mother beginning several weeks before delivery. Fetal scalp vein platelet count determinations have been suggested as one means to assess the fetal platelet count. Because thrombocytopenia is rare in the infant and because cesarean section poses a risk to the thrombocytopenic mother, some authors conclude that a vaginal delivery should be undertaken with immediate and frequent monitoring of the newborn's platelet count.

Thrombotic Thrombocytopenic Purpura and Related Disorders

MECHANISM AND DIAGNOSIS

TTP, hemolytic uremic syndrome (HUS), and HELLP (microangiopathic *h*emolysis, *e*levated *l*iver function tests, *l*ow *p*latelet counts) syndrome (Chapter 72) represent a clinical spectrum of the same pathogenic event occurring in different patient subgroups.

The hemolysis in TTP is due to red cell shearing in the microvasculature, from platelet thrombi. Von Willebrand factor (VWF) is initially produced as a large multimeric protein, or *ultra-large VWF multimer (ULVWF).* Normally, this ULVWF is cleaved by a protease specific

BOX 63.3 ■ Differential Diagnosis of Thrombocytopenia with Microangiopathy

TTP (thrombotic thrombocytopenic purpura)
HUS (hemolytic uremic syndrome)
DIC (disseminated intravascular coagulation)
HELLP (hemolytic anemia, elevated liver function tests, low platelet counts)
Malignant hypertension
Preeclampsia, eclampsia
Septic abortion
Systemic vasculitis
Carcinoma
Solid organ rejection
Mitomycin C, cisplatin, cyclosporine
Cholesterol emboli syndrome

for VWF named ADAMTS13 (a disintegrin and metalloprotease with thrombospondin 1–like domains). In the majority of cases, the lack of ADAMTS13 leads to an accumulation of ULVWF, which in turn has a greater propensity to activate platelets, leading to the formation of platelet thrombi and occlusion of the microcirculation. Box 63.3 lists the differential diagnosis for thrombocytopenia with microangiopathy.

Patients with TTP typically present with the relatively abrupt onset of several or all of the following *classic pentad* of cardinal signs and symptoms: (1) fever, (2) mucosal bleeding resulting from thrombocytopenia, (3) altered central nervous system function (which may manifest itself only as a headache), (4) renal dysfunction or hematuria, and (5) hemolytic anemia resulting from a microangiopathic process (this is also called *microangiopathic hemolytic anemia* [MAHA]). The diagnosis of TTP does not require all five findings, but all patients diagnosed with TTP must manifest microangiopathy. This condition occurs when erythrocytes are fragmented by strands of fibrin deposited in the microvasculature (see Figure 45.1 in Chapter 45).

HUS is similar to TTP, but neurologic dysfunction is absent or mild, whereas renal dysfunction is more pronounced. HUS also does not manifest a low ADAMTS13 level, unlike TTP. HUS is often secondary to infections by Shiga toxin–producing bacteria such as *Escherichia coli* O157:H7. HELLP syndrome occurs in pregnant or peripartum patients and is probably part of the spectrum of preeclampsia (Chapter 72). TTP and related disorders are true emergencies and must be managed as such.

A definitive diagnosis is made on clinical grounds, but it is supported by inspection of the peripheral blood smear. Patients with TTP and related disorders have schistocytes (fragmented blood cells) (usually many schistocytes) on their smears (Figure 45.1). Microangiopathic hemolytic anemia (MAHA) and thrombocytopenia are consistent abnormalities present in TTP but can also be observed in other conditions. In fact, the landmark trial that demonstrated the efficacy of plasma exchange therapy had these two criteria as the only required abnormalities for the diagnosis of TTP. In addition, patients with microangiopathy also have low platelet counts and nucleated red blood cells. The reticulocyte count is usually elevated unless the bone marrow has been infarcted. Lactate dehydrogenase (LDH) levels are elevated because of intravascular destruction of red blood cells, with release of their stores of intracellular LDH. As such, serial LDH levels are useful markers of disease activity.

ADAMTS13 assays are not routinely or immediately available, therefore they should only be used as an aid in the diagnosis. In addition, there is wide variation in specificity and sensitivity of this assay for idiopathic TTP. Severe ADAMTS13 deficiency may also occur in disorders other than TTP, and a normal ADAMTS13 activity cannot be used to rule out a diagnosis of TTP.

TREATMENT

Platelet transfusions must *not* be given to patients with TTP. They should be avoided for all but life-threatening bleeding. The problem with platelet transfusions is that they have been associated with sudden death resulting from microthrombosis in vital organs, such as the heart and brain. Primary therapy of TTP remains plasma exchange via apheresis therapy. Initially, patients should have a daily exchange of 1 to 2 plasma volumes. Removed plasma is usually replaced with fresh frozen plasma in patients with TTP in contrast to the use of albumin as replacement protein for other categories of disease, such as acute Guillain-Barré syndrome (Chapter 67). This avoids the coagulopathy resulting from removal of clotting factors by the apheresis therapy.

However, replacement with plasma deficient in high molecular weight von Willebrand multimers (cryosupernatant) may also be used. Cryosupernatant replacement has not been shown to be superior to plasma replacement. The optimal number and total duration of plasma exchanges for the treatment of TTP remain unclear. Plasma exchange usually continues daily until the patient improves clinically and the platelet count improves. When the platelet count and LDH levels normalize, the plasma exchange is gradually tapered. Each plasma exchange costs about $1000, and the overall response rate is about 80%. The effectiveness of plasma exchange has been attributed to the removal of ADAMTS13 autoantibodies and replacement of ADAMTS13 activity, even though it is also effective in patients who do not have a severe deficiency of ADAMTS 13.

Plasma exchange has associated risks that should be noted. In an important cohort study of 206 patients, there was a 2% mortality and 26% morbidity associated with plasma exchange therapy for TTP. However, the prognosis for TTP prior to apheresis was very poor with an estimated 90% mortality in some series.

Glucocorticoids are administered to all patients with TTP at a dose equivalent to prednisone of 1 mg/kg/day. Although randomized trials have not established the true benefit of daily steroid administration, the response rate of TTP to prednisone alone is about 10%, and there may be a potential additive effect with plasma exchange therapy. The adjunctive use of antiplatelet agents such as aspirin, dipyridamole, or sulfinpyrazone should be avoided because they may increase the risk of bleeding.

Before establishment of plasma exchange as the primary treatment modality for TTP, splenectomy and glucocorticoid administration were often used as combination therapy. Despite increased complications from thrombocytopenia, experienced surgeons can usually perform splenectomies in patients with TTP safely, with a response rate as high as 50%. Early splenectomy was associated with a better response rate than splenectomy that was performed late in the course of TTP, but this difference may only reflect selection bias. Splenectomy may prevent subsequent episodes of TTP.

Other agents, including vincristine (2 mg weekly), azathioprine, cyclophosphamide, and IVIG, have been used anecdotally in the treatment of TTP with varied success. Most patients with TTP survive, but the mortality rate is still significant at about 20%. Relapses commonly occur in survivors. These are treated similarly to initial bouts of TTP.

Rituximab, a chimeric anti-CD-20 antibody with immunosuppressive proprieties, mainly used in the treatment of clonal B cell disorders, has been used in cases of refractory or recurrent TTP. However, most of the data regarding the use of rituximab in TTP are in the form of case reports and small case series and, therefore, are of unclear efficacy.

ASSOCIATED DISORDERS

HUS is more prevalent than TTP in young children. In many cases, HUS is preceded by bloody diarrhea from verotoxin-producing bacteria such as *E. coli* O157:H7 or *Shigella dysenteriae*

type 1. Patients with HUS become anuric and may have seizures. Most patients recover with supportive measures only, although plasma exchange has also been used with apparent success.

Other conditions such as cancer have been associated with TTP-like illnesses. The malignancy is usually widely metastatic, and treatment of the underlying malignancy usually resolves the TTP. Chemotherapeutic drugs, such as mitomycin C or, less commonly, cisplatin and gemcitabine, have also been associated with TTP. Other drugs such as cyclosporine, FK506 (tacrolimus [Prograf]), quinine, and cocaine have been associated with TTP. Clopidogrel and the related drug ticlopidine, antiplatelet agents widely used in interventional cardiology, have been associated with TTP that usually occurs in the first 2 weeks of therapy. Treatment consists of removal of the offending drug and consideration of plasma exchange.

Summary

A careful history and physical examination and the review of the peripheral blood smear will usually allow the diagnosis of ITP or TTP. However, most patients with thrombocytopenia in the ICU will have low platelet counts that result from other causes, such as sepsis, liver disease with hypersplenism, heparin or other drugs, or disseminated intravascular coagulation (see Chapter 45). A high index of suspicion and hematologic consultation will permit the ICU clinician to differentiate these more common causes of thrombocytopenia from the less common disorders of ITP and TTP, leading to their successful diagnosis and treatment.

An annotated bibliography can be found at www.expertconsult.com.

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Froissart A, Buffet M, Veyradier A, et al: Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with a suboptimal response to plasma exchange. Experience of the French Thrombotic Microangiopathies Reference Center. Crit Care Med 40:104-111, 2012. doi: 10.1097/CCM.0b013e31822e9d66. http://www.ncbi.nlm.nih.gov/pubmed/21926591.

This was a small prospective study suggesting that rituximab is effective in both producing remission in patients with TTP and reducing TTP relapse when compared to historical controls treated with plasma exchange.

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Moatti-Cohen M, Garrec C, Wolf M, et al: Unexpected frequency of Upshaw-Schulman syndrome in pregnancy-onset thrombotic thrombocytopenic purpura. Blood 119:5888-5897, 2012. doi: 10.1182/blood-2012-02-408914. Epub 2012 Apr 30. http://www.ncbi.nlm.nih.gov/pubmed/22547583.

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Moschowitz E: An acute pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries: an undescribed disease. Arch Intern Med 36:89-93, 1925.

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Patel VL, Mahévas M, Lee SY, et al: Outcomes 5 years after response to rituximab therapy in children and adults with immune thrombocytopenia. Blood 119:5989-5995, 2012. doi: 10.1182/blood-2011-11-393975. Epub 2012 May 7. http://www.ncbi.nlm.nih.gov/pubmed/22566601.

This study suggested that a quarter of adults and children with chronic ITP treated with rituximab remain in remission at 5 years without major toxicity.

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This prospective study suggested that rituximab combined with standard plasma exchange is better than plasma exchange alone when compared with historical controls.

CHAPTER 64

Acute Central Nervous System Infections

Stephen J. Gluckman

Acute infections of the central nervous system (CNS) are generally categorized as meningitis or encephalitis. Although it may be difficult to differentiate between them in some patients, the difference in their diagnostic considerations and therapeutic approaches is important. *Encephalitis* refers primarily to a brain parenchymal infection characterized by a clinical presentation of cerebral dysfunction—for example, obtundation, confusion, focal abnormalities, or a combination of these conditions. Encephalitis is most commonly caused by viruses. In *meningitis*, initial abnormalities usually include fever, headache, and meningeal signs. If cerebral dysfunction does occur with meningitis, it is the secondary result of cerebral edema, increased intracerebral pressure, alterations in cerebral blood flow, or a combination of these factors. Although most cases of meningitis are due to viruses or bacteria, some may be due to noninfectious agents. One subset of meningitis is *aseptic meningitis.* This refers to meningitis in which no common bacterial pathogen can be identified. Although most patients with aseptic meningitis are not ill enough to be admitted to an intensive care unit (ICU), occasionally the cause of the CNS disease is in doubt or patients are unusually ill. This chapter focuses on acute syndromes of meningitis and encephalitis with an onset of hours to a few days.

Epidemiology and Etiology

VIRAL CENTRAL NERVOUS SYSTEM INFECTIONS

Most CNS viral pathogens are more closely associated with either a meningitis syndrome or an encephalitis syndrome; considering the syndrome will influence the evaluation and treatment. Enteroviruses are the most common causes of the former and arboviruses the latter. However, there can be some clinical overlap. In the past, the specific cause of cases of presumed viral CNS infections were often undetermined. However, newer diagnostic techniques, particularly the use of the polymerase chain reaction (PCR), have resulted in the identification of a pathogen in up to 55% to 70% of cases.

BACTERIAL CENTRAL NERVOUS SYSTEM INFECTIONS

Uncomplicated adult bacterial meningitis in the United States is primarily due to *Streptococcus pneumoniae* and *Neisseria meningitidis*. However, many factors influence the likelihood of infection with other organisms (Table 64.1). Splenectomy, immunoglobulin deficiency, pneumococcal pneumonia, alcoholism, chronic liver or renal disease, diabetes mellitus, and cerebrospinal fluid leaks all predispose the patient to infection with *S. pneumoniae*. Agents causing meningitis in the postneurosurgical or head trauma setting include staphylococci and gram-negative bacilli. *Listeria monocytogenes* should be considered in persons with a defect in cell-mediated immunity (e.g., solid organ transplant, human immunodeficiency virus [HIV] infection, chronic

TABLE 64.1 ■ **Predisposing Factors to Specific Bacterial Meningitis Pathogens**

Predisposing Factor	Pathogens
Age	
Young adult	*Neisseria meningitidis*
Adult (any age)	*Streptococcus pneumoniae*
Older adult	*Listeria monocytogenes*
Impaired Host Defense	
Granulocytopenia	Aerobic gram-negative bacilli, *Staphylococcus aureus*
—Defect in cell-mediated immunity	*L. monocytogenes*
—Terminal complement deficiency	*N. meningitidis*
Postsplenectomy	*S. pneumoniae*
Open head trauma, postneurosurgery	Aerobic gram-negative bacilli, *S. aureus, S. epidermidis*
Cerebrospinal fluid shunt	*S. epidermidis*
Basilar skull fracture	*S. pneumoniae*

corticosteroid use, Hodgkin disease), as well as in alcoholics, the elderly, and persons with iron overload, chronic liver or renal disease, and diabetes.

Pathogenesis

Acute meningitis and encephalitis are primarily caused by relatively few pathogens with unique abilities to invade the cerebrospinal fluid (CSF). As a rule, viral and bacterial CNS pathogens gain entry into the CSF via a hematogenous route. However, some viruses may also gain access by retrograde spread along nerves, and some bacteria occasionally invade the CNS from a contiguous focus or by direct inoculation during or after trauma or neurosurgery.

In bacterial meningitis, once these agents gain access to the CSF fluid, few host defenses are available to control their rapid multiplication. CSF is devoid of phagocytic cells or effective humoral immunity via immunoglobulins or complement. The pathogens induce an inflammatory response that is mediated by a number of cytokines within the CSF, particularly interleukins 1 and 6 and tumor necrosis factor. These cytokines induce phagocytes to adhere to endothelium and enter the CSF. The resultant inflammation and microvascular injury produces brain edema, increased intracerebral pressure, decreased tissue perfusion, and direct tissue injury. Improved understanding of this pathogenesis has led to considerations for therapeutic intervention with drugs that can modulate the inflammatory response.

Viral encephalitis can be either *primary* or *postinfectious*. Primary infection is characterized by direct viral invasion of the CNS, which can be demonstrated by light or electron microscopy. The virus can often be cultured from brain tissue or identified by immunofluorescent staining. In postinfectious encephalitis, the virus cannot be detected in tissue or recovered in culture. Although the neurons are not involved, perivascular inflammation and demyelination are prominent.

Clinical Presentation and Complications

Most patients with *acute viral meningitis* present with fever, headache, and nuchal rigidity. The headache is typically severe and either frontal or diffuse. Photophobia is also common. Meningismus limits head flexion but not rotation. In contrast, both flexion and rotation are limited in patients with cervical arthritis, Parkinson disease, and neuroleptic malignant syndrome. Additional symptoms might include nausea, vomiting, diarrhea, and myalgias. Patients with viral meningitis are usually

uncomfortable but do not appear toxemic. Although most patients have a nonspecific presentation, associated clinical clues to the cause might include an enteroviral exanthem, mumps parotitis, or herpes genitalis. The duration of viral meningitis is generally less than a week, and it usually resolves without sequelae.

Acute bacterial meningitis also presents with fever, headache, and findings of meningeal irritation. In addition, an altered sensorium with a nonfocal neurologic examination can rapidly develop. Mental status derangement can vary from mild confusion to complete unresponsiveness. If these symptoms occur, focal neurologic findings include cranial nerve palsies, hemiparesis, and aphasia. They are often associated with complications such as subdural empyema, cortical vein thrombosis, sagittal or cavernous sinus thrombosis, or hydrocephalus. Focal or generalized seizures may also occur. Because papilledema is *not* a feature of uncomplicated meningitis, this finding suggests the presence of a complication or an alternative diagnosis.

In certain groups of patients, the presentation of bacterial meningitis is more likely to be atypical. Meningitis in the elderly may be subtle with only a change in mental status. In patients who have sustained head trauma, the findings of an associated meningitis may be attributed to the injury. In neutropenic patients, the inflammatory response in the CSF may be attenuated. For these reasons, bacterial meningitis must be considered in any patient with an altered mental status, especially if febrile.

The general physical examination may occasionally give clues to the cause of the bacterial meningitis. A localized source of infection, such as pneumonia or sinusitis, may be found. Characteristic cutaneous findings of meningococcemia—that is, petechiae or purpura—suggest that organism, but these findings can also be seen with other pathogens. Other possible clues include the presence of a CSF shunt, sinusitis, or CSF rhinorrhea.

The primary initial distinction between viral and bacterial CNS infections is based on the cerebrospinal fluid analysis. The clinical distinction between viral meningitis and encephalitis is based on the state of brain function. Patients with viral meningitis may be uncomfortable, lethargic, or distracted by headache, but their cerebral function remains normal. Abnormalities in brain function in encephalitis, however, are expected and include altered mental status, motor or sensory deficits, and speech or movement disorders. Seizures and postictal states can be seen with meningitis alone and should not be construed as definitive evidence of encephalitis. Encephalitis with herpes simplex virus type 1 (HSV-1) has a particular affinity for the medial temporal and inferior frontal lobes of the brain. For this reason, symptoms such as bizarre behavior, speech disorders, and gustatory or olfactory hallucinations are characteristic of infection with this organism. Accompanying herpes labialis is seen in less than 10% of cases. Furthermore, the appearance of herpetic skin lesions can be a nonspecific complication of many febrile illnesses. Therefore, the presence or absence of mucocutaneous herpes infection is *not* of diagnostic importance in evaluating patients for HSV-1 encephalitis.

General Diagnostic Approach

Examination of the CSF obtained by lumbar puncture is the key initial test in the evaluation of a patient for CNS infection. The CSF should routinely be sent for cell count and differential, glucose and protein determinations, Gram stain, and bacterial culture. These CSF findings will confirm or rule out the presence of CNS inflammation. Although the specific pattern of results will also generally allow the clinician to distinguish a bacterial from a nonbacterial process, the routine CSF findings in viral meningitis, other causes of aseptic meningitis, and viral encephalitis are indistinguishable.

In most patients, the presentation of an acute meningitis is sufficiently distinct from the presentation of a CNS mass lesion that imaging before a lumbar puncture is unnecessary and might potentially delay therapy (Figure 64.1). A number of historical and physical examination findings

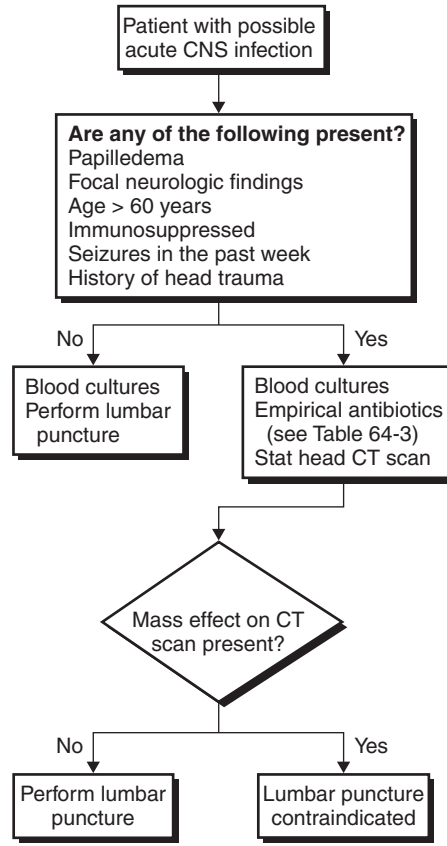


Figure 64.1 Schematic flow diagram outlining steps in the initial evaluation of a patient suspected of having an acute central nervous system (CNS) infection (see text for details). CT, computed tomography.

have been shown to increase the likelihood of a CNS mass lesion and should prompt either computed tomography or magnetic resonance imaging of the brain before lumbar puncture. These include age > 60, immunosuppressed state, recent seizure, altered mental status, papilledema, focal neurologic findings, or evidence of head trauma. If meningitis is a consideration but the presence of any of these findings suggest the possibility of a focal CNS problem, *antibiotic therapy should not be delayed while obtaining CNS imaging studies before lumbar puncture*. In addition to the initial tests mentioned earlier, several milliliters of CSF should be saved in a refrigerator pending the results of these initial tests in case further testing is needed. Generally the results of the initial tests reflect whether or not the process is bacterial (Figure 64.2). If bacterial meningitis is not diagnosed, this reserved fluid can be tested for other pathogens.

The CSF findings in patients with viral and bacterial CNS infections are shown in Table 64.2. In *viral meningitis* or *encephalitis,* the predominant cell is the lymphocyte, although early in the course granulocytes (neutrophils) may be in the majority. In equivocal situations, a repeat CSF examination 8 hours after the first will show a shift from granulocytes to lymphocytes in most cases. The CSF glucose level is usually normal, but a mild decrease can be seen with HSV, mumps, some enteroviruses, and lymphocytic choriomeningitis virus. The presence of red blood cells in the appropriate setting suggests HSV-1 encephalitis.

In *bacterial meningitis,* the white blood cell count is expected to be > 1000 cells/μL, but lower values are occasionally seen. CSF with < 10 white blood cells/μL has a 99% negative predictive value for bacterial meningitis (in non-neutropenic patients). In most bacterial cases > 90% of the

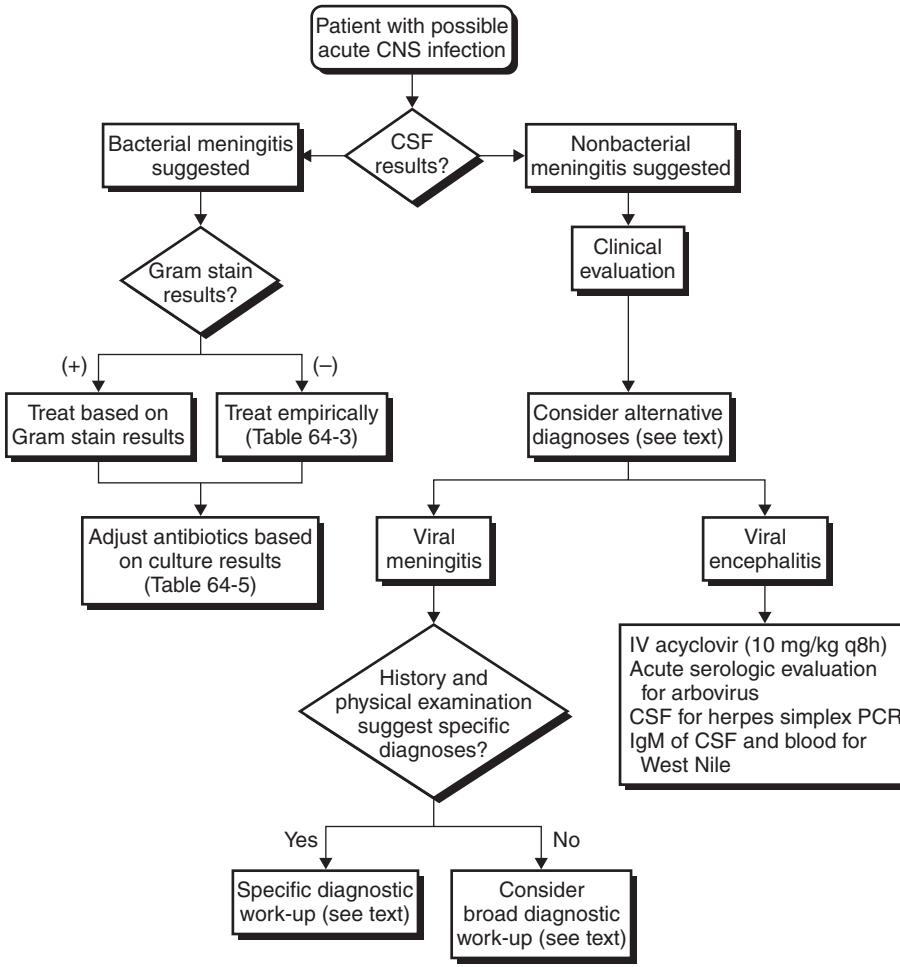


Figure 64.2 Schematic flow diagram outlining steps in the evaluation of a patient suspected of having an acute central nervous system (CNS) infection based on the initial results of cerebrospinal fluid (CSF) analysis (see Table 64.2 and text for details). IV, intravenous; PCR, polymerase chain reaction; IgM, immunoglobulin M.

TABLE 64.2 ■ **Typical Cerebrospinal Fluid Findings in Viral and Bacterial Meningitis**

	Viral	Bacterial
WBCs (cells/μL)	< 1000	> 1000
% Granulocytes	< 50*	> 90
Glucose	Normal†	Decreased
Protein	Elevated	Elevated
Gram stain	Negative	Positive in 80%–90% of cases

*Early in viral meningitis there may be a predominance of granulocytes.
†See text for a discussion of normal and decreased values.
WBCs, white blood cells.

cells are granulocytes. A lymphocyte predominance may be seen when the total count is low. This is most commonly due to infection with *L. monocytogenes*. A decreased CSF glucose concentration is expected but is not specific for bacterial meningitis. It can also be seen in carcinomatous meningitis, tuberculous meningitis, some viral meningitides, or when the serum glucose is low. A decreased CSF glucose level in bacterial meningitis is due to both anaerobic glycolysis and a decrease in its active transport. CSF glucose values of < 10 mg/dL are highly specific for bacterial meningitis but are uncommon. CSF glucose levels are < 40 mg/dL in 60% and a ratio of CSF:serum glucose is < 0.3 in 70% of cases of bacterial meningitis. Since values for cell count, percentage of granulocytes, and glucose can individually overlap with aseptic meningitis, it is important to look at the entire pattern when evaluating the CSF results. However, CSF glucose levels of < 34 mg/dL, a CSF:serum glucose ratio of < 0.3, a CSF protein concentration > 220 mg/dL, a CSF white blood cell count > 2000/μL, and a CSF granulocyte count > 1180/μL were found to be independent predictors of bacterial rather than viral meningitis with a specificity of 99%. Because CSF bacterial antigen tests are no more sensitive than is the CSF Gram stain, the routine use of these tests in adults is generally not indicated. They are potentially useful, however, in a patient who was started on antibiotics before the initial lumbar puncture.

Approach to the Patient with a Presumed Nonbacterial Central Nervous System Infection

The general approach to a *nonbacterial* CNS infection is outlined in Figure 64.1. With the exception of HSV-1, human immunodeficiency virus (HIV), and possibly varicella, there are no specific drugs for viral CNS infections. Because of these limited therapeutic implications, the approach to a patient with clinical and CSF features of viral meningitis or encephalitis should be limited to the following:

1. *Empirical treatment for HSV-1 with acyclovir if there is evidence of encephalitis.* Early treatment is clearly associated with a better outcome. The dose is 10 mg/kg intravenously (IV) every 8 hours in patients with normal renal function. The duration is 10 to 14 days.
2. *Careful consideration for another, potentially treatable cause* (e.g., nonsteroidal anti-inflammatory drug-associated sterile meningitis, dural sinus thrombosis, CNS vasculitis, syphilitic meningitis, Lyme meningitis, limbic encephalitis).
3. *Observation for clues of specific viruses.* A focal encephalitis, especially with localization to the temporal lobes by electroencephalography, computed tomography, or magnetic resonance imaging suggests infection with HSV-1. Other enteroviral illnesses in the home (as suggested by illnesses with pleurodynia, pancreatitis, parotitis, or febrile exanthem) suggest an enteroviral meningitis. Parotitis suggests mumps or enteroviral infection. Measles and varicella are associated with characteristic rashes. Recent high-risk exposure suggests possible acute HIV infection. Nonfocal weakness, occasionally profound, is a common finding of CNS infection resulting from West Nile virus.
4. *The pursuit of a viral cause other than HSV should be individualized, depending on the clinical information as indicated in the following sections.* Although there is no specific treatment for most viruses, patients and their families often benefit from an explanation of an illness as severe as meningitis or encephalitis:
   a. When HSV-1 is a consideration, request a CSF polymerase chain reaction for HSV. This is the most rapid and specific test available and has replaced other modalities. Brain biopsy can establish the diagnosis, but there are occasionally false-negative results. CSF culture has a low sensitivity. Measurement of serum HSV antibodies is not helpful.
   b. Polymerase chain reaction on CSF, blood, and stool for enteroviruses has replaced culture. HSV-2 can also be diagnosed by PCR testing.

c. Obtain routine serologic studies for HIV, although the serologic results are often negative at the time of presentation with acute HIV infection. Seroconversion occurs several weeks later with recovery. In contrast, PCR for HIV is positive in high titer during acute disease.
d. Obtain an "acute" serologic profile for the arboviruses (including West Nile virus) to be paired with a "convalescent" blood study 2 to 3 weeks later. CSF and serum should also be sent for specific IgM antibodies to West Nile virus. Mumps can be also diagnosed by finding specific IgM antibodies in addition to PCR on CSF and viral culture of CSF or saliva.

Approach to the Patient with a Presumed Bacterial Central Nervous System Process

When CSF examination suggests a bacterial process, empirical antibiotics are indicated until the culture results are known. The initial choice should be guided by the findings on the CSF Gram stain and any specific clinical features that might alter the microbiologic picture (Tables 64.3 and 64.4; see also Table 64.1).

TABLE 64.3 ■ **Initial Empirical Therapy of Presumed Bacterial Meningitis**

Clinical	Antibiotic
Adult < 50 years with no predisposing factors	Ceftriaxone or cefotaxime plus vancomycin
Adult > 50 years	Same as above plus ampicillin
Decreased cell-mediated immunity*	Same as above plus ampicillin
After head trauma or neurosurgery	Ceftazidime plus vancomycin
Granulocytopenia	Ceftazidime plus vancomycin
Cerebrospinal fluid shunt infection	Ceftriaxone or cefotaxime plus vancomycin

*Examples include patients receiving steroids chronically, with lymphoma, HIV disease, or solid organ transplant.

TABLE 64.4 ■ **Recommended Doses of Antibiotics for Bacterial Meningitis in Adults with Normal Renal and Hepatic Function (see Chapter 17 for dose adjustments in renal and other organ failure)**

Antibiotic	Dose (Total/Day)	Dosing Interval (Hours)
Amikacin	15 mg/kg	8
Ampicillin	12 g	4
Cefotaxime	12 g	4
Ceftazidime	6 g	8
Ceftriaxone	4 g	12
Chloramphenicol	4–6 g	6
Ciprofloxacin	800 mg	12
Gentamicin	5 mg/kg	8†
Nafcillin	12 g	4
Penicillin G	20–24 million units	4
Rifampin	600 mg	24
Trimethoprim-sulfamethoxazole	20 gm/kg*	12
Vancomycin	2 g	12†

*Dosage based on the trimethoprim component.
†Adjust dose by serum level (see Chapter 17).

TABLE 64.5 ■ **Specific Antimicrobial Therapy for Bacterial Meningitis**

Organism	Standard Therapy	Alternative Therapies
Streptococcus pneumoniae		
Sensitive to penicillin (mean inhibitory concentration [MIC] < 0.1 μg/mL)	Penicillin G	Third-generation cephalosporin,* chloramphenicol, cefuroxime
S. pneumoniae		
Resistant to penicillin		
(MIC = 0.1–1 μg/mL)	Third-generation cephalosporin	Vancomycin
(MIC > 2 μg/mL)	Vancomycin	
Neisseria meningitidis	Penicillin G	Third-generation cephalosporin, cefuroxime, chloramphenicol
Haemophilus influenzae		
Beta-lactamase (–)	Ampicillin	Third-generation cephalosporin, chloramphenicol, cefuroxime
Beta-lactamase (+)	Third-generation cephalosporin	Chloramphenicol, fluoroquinolone†
Enterobacteriaceae	Third-generation cephalosporin	Piperacillin, chloramphenicol, trimethoprim-sulfamethoxazole
Listeria monocytogenes	Ampicillin‡	Trimethoprim-sulfamethoxazole
Pseudomonas aeruginosa	Ceftazidime‡	Piperacillin,‡ fluoroquinolone,† imipenem‡
Staphylococcus aureus		
Methicillin sensitive	Nafcillin or oxacillin	Vancomycin
Methicillin resistant	Vancomycin	Trimethoprim-sulfamethoxazole
S. epidermidis	Vancomycin§	

*Ceftriaxone, cefotaxime, ceftazidime.
†Levofloxacin, ofloxacin, ciprofloxacin, and others.
‡The addition of an aminoglycoside should be considered (see text).
§The addition of rifampin should be considered (see text).

Once a specific bacterial cause of meningitis has been identified by culture, the antimicrobial regimen can be modified (Table 64.5). *Pseudomonas aeruginosa* should be treated with ceftazidime (or an antipseudomonal penicillin) plus an aminoglycoside. If there is no response to systemic therapy, consideration should be given to intrathecal or intraventricular aminoglycoside dosing. Many clinicians add an aminoglycoside to the regimen in patients with proven *Listeria* meningitis because of in vitro synergy (although improved in vivo efficacy has not been demonstrated). *Staphylococcus epidermidis*, the predominant pathogen in CSF shunt infections, should be treated with vancomycin. Rifampin has been added in patients who do not improve. Although some persistent shunt infections have been cured when vancomycin has been injected directly into the shunt, in general, the shunt must be removed under these circumstances.

In a patient with a history of a severe allergy to penicillin, chloramphenicol should be substituted, though there have been treatment failures. An attempt to desensitize the patient to penicillin or cephalosporins should be made if the patient is not responding (Chapter 32).

Although the duration of antimicrobial therapy for bacterial meningitis has not been scientifically determined, 10 to 14 days is standard for pneumococcus, meningococcus, and hemophilus. Gram-negative meningitis and meningitis resulting from *L. monocytogenes* is usually treated for 3 weeks.

Adjunctive Therapy

1. If there are signs of increased intracranial pressure (ICP), treatment to lower it should be started and monitoring ICP invasively should be considered in severe cases (see Chapter 41).
2. Fever increases brain metabolic activity. This, in turn, increases cerebral blood flow, which may have detrimental effects by raising ICP. Antipyretic agents should be used to keep the temperature less than 38.0° C.
3. The inappropriate secretion of antidiuretic hormone commonly complicates intracerebral infections. One should follow serum electrolyte levels attentively and adjust fluid management appropriately to avoid hyponatremia (see Chapter 84) because this will exacerbate brain edema.
4. Recurrent seizures can produce neuronal damage and should be controlled. Prophylactic antiseizure therapy, however, is not indicated.
5. Adjunctive corticosteroids should be considered. The rapid bactericidal activity of many of the antibiotics causes lysis of bacteria, which provokes the release of proinflammatory mediators. Because these mediators have the potential to increase inflammation and brain injury, blunting the inflammatory response has a sound rationale.

   Clinical studies investigating the benefits of adjunctive treatment with dexamethasone for bacterial meningitis in adults have yielded conflicting results in the developed and the developing world. There appears to be a proven benefit for steroid use in the treatment of pneumococcal meningitis in the developed world, but no benefit in the developing world. This might be due to the much higher incidence of co-infection with HIV in the developing world or less-well-developed supportive care. If there is to be a benefit, steroids must be administered either before or at the time of initiation of antibiotics. Because the specific bacterial etiology is rarely known at the time antibiotics are initiated, it is reasonable to give dexamethasone, 0.15 mg/kg IV every 6 hours for 4 days in HIV-negative persons. Some clinicians would discontinue steroids if an organism other than pneumococcus grows; others would not.

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CHAPTER 65

Community-Acquired Pneumonia

David A. Oxman ■ Marissa B. Wilck

Pneumonia is defined as inflammation and consolidation of lung tissue resulting from an infectious agent. The eighth leading cause of death and responsible for more than 60,000 deaths annually in the United States, pneumonia is the most common infectious disease resulting in mortality. Although newer antimicrobial agents have been developed to treat community-acquired pneumonia (CAP), the incidence of this disease resulting from resistant pathogens continues to rise. Finally, increased populations at high risk, particularly those with acquired immunodeficiency disease or those receiving immunosuppressive therapy, contribute to the increasing importance of opportunistic pathogens as causes of CAP.

As a general rule, CAPs are present upon hospital admission or occur within the first 48 hours after admission—the latter were incubating at time of admission. In contrast, according to the American Thoracic Society's (ATS) guidelines, health care–associated pneumonias (HCAPs) are defined as those that occur 48 hours or later after admission to a health care facility and were not incubating at the time of admission. However, pneumonias that are present upon hospital admission or shortly thereafter but occur in nonambulatory residents of a nursing home or other long-term care facility should be regarded as HCAPs and managed as such (see Chapter 14).

Clinical Diagnosis and Causes

Although the majority of patients with CAP present with the classic signs and symptoms of fever, cough, and sputum production, these signs and symptoms are neither sensitive nor specific. For example, elderly patients with CAP often show none of these traditional indicators of infection. Instead, the most reliable sign of pneumonia in this group is an increased respiratory rate.

ATYPICAL VERSUS TYPICAL PNEUMONIA

Historically, some clinicians distinguished *typical* and *atypical* CAP based on clinical presentation. CAP caused by "atypical" organisms (*Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella* species, and viruses) was thought to be characterized by a prior viral-like syndrome (myalgias, arthralgias, and sore throat), subacute time course, nonproductive cough, absence of pleurisy and rigors, lower fever, and absence of consolidation on auscultation compared with CAP caused by "typical" organisms (*Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus,* and gram-negative bacteria). When studied systematically, however, these characteristics were no more common in atypical than in typical pneumonias. In addition, comparing laboratory data and chest radiographs failed to discriminate between patients with typical and atypical pneumonias. Clinical demographics may give clues to the cause, but definitive diagnosis depends on laboratory and microbiologic testing to identify a specific pathogen.

PATHOGENS

Many different organisms cause CAP. Although the isolation rate has decreased, *S. pneumoniae* (pneumococcus) remains the most frequently identified cause of CAP. Yet despite new diagnostic techniques, the cause of CAP remains unknown in up to 45% of cases. The most common pathogens identified (in descending order of frequency) are *S. pneumoniae, H. influenzae, M. pneumoniae, C. pneumoniae,* respiratory viruses, and *Legionella* species. The most common organisms in patients admitted to the intensive care unit (ICU) vary from all patients with CAP. For example, a review of nine studies that included 890 patients with CAP who were admitted to the ICU between 1999 and 2001 reported that the most common pathogens in the ICU population were (in descending order of frequency) *S. pneumoniae, Legionella* species, *H. influenzae,* Enterobacteriaceae species, *S. aureus,* and *Pseudomonas* species. About 20% of CAP in ICU patients may be due to atypical, most likely *Legionella,* species.

Because initial CAP treatment is often empirical, knowledge of the most likely pathogens is vital. The causative organism may be suspected based on the patient's risk factors or comorbid illnesses (Table 65.1). *S. pneumoniae,* however, remains the most common cause in *all* groups including those with human immunodeficiency virus (HIV). Severe recurrent pneumonias with *S. pneumoniae* or *H. influenzae* suggest an underlying immunocompromised state—for example, HIV infection or multiple myeloma. *Legionella* infections by non-*pneumophila* species may also be more common in immunosuppressed patients and warrant assessment of the patient's immune status. Viruses may cause up to 30% of CAP. Although the most prevalent respiratory virus is influenza, others such as adenovirus, respiratory syncytial virus (RSV), and parainfluenza are also common.

Diagnostic Evaluation

CHEST RADIOGRAPH

When CAP has a typical clinical presentation, an infiltrate on chest radiograph confirms the diagnosis. The chest radiograph may be normal, however, if taken in the first 24 hours of a bacterial pneumonia or in the setting of severe neutropenia. Likewise, an estimated 30% to 40% of patients with *Pneumocystis jiroveci* (previously named *P. carinii*) pneumonia may have normal-appearing chest radiographs at presentation.

GRAM STAIN AND CULTURE OF SPUTUM

Although its value has been widely debated, a Gram stain and culture of expectorated sputum may establish the cause of CAP and guide initial therapy. Although only 60% to 70% of patients with CAP can produce sputum on hospital admission, these sputum tests are non-invasive and relatively inexpensive. In patients eventually diagnosed with pneumonia resulting from *S. pneumoniae,* 62% to 89% demonstrate lancet-shaped gram-positive diplococci on initial Gram stain. Alternatively, finding many polymorphonuclear neutrophils and no organisms on Gram stain suggests infection with *M. pneumoniae, C. pneumoniae,* or *Legionella* species.

Sputum cultures *must* be interpreted in light of the findings of the corresponding sputum Gram stain. Isolation of a predominant organism by culture is clinically compelling when compatible with the Gram stain findings. Isolation of a predominant organism that is not part of the normal respiratory flora may be useful in modifying antibiotics. Similarly, failure to find organisms such as *S. aureus* or gram-negative bacilli on Gram stain or in culture suggests they are truly absent. Because of difficulty in isolation, cultures for *M. pneumoniae, C. pneumoniae, Legionella* species, and respiratory viruses are not routinely performed.

The clinical value of a sputum Gram stain and culture depends largely on the quality of the sputum specimen. Having > 25 polymorphonuclear neutrophils and < 10 squamous

TABLE 65.1 ■ **Commonly Encountered Pathogens for Community-Acquired Pneumonia According to Specific Conditions or Risk Factors**

Condition	Commonly Encountered Pathogen(s)
Alcoholism	*Streptococcus pneumoniae,* oral anaerobes, *Klebsiella pneumoniae, Acinetobacter* species, *Mycobacterium tuberculosis*
Aspiration	Gram-negative enteric pathogens, oral anaerobes
COPD or smoking	*Haemophilus influenzae, Pseudomonas aeruginosa, Legionella* species, *S. pneumoniae, Moraxella catarrhalis, Chlamydophila pneumonia*
Cough for 12 weeks with whoop or posttussive vomiting	Bordetella pertussis
Endobronchial obstruction	Anaerobes, *S. pneumoniae, H. influenzae, Staphylococcus aureus*
Exposure to bat or bird droppings	*Histoplasma capsulatum*
Exposure to birds	*Chlamydophila psittaci* (if poultry: avian influenza)
Exposure to farm animals or parturient cats	*Coxiella burnetii* (Q fever)
Exposure to rabbits	*Francisella tularensis*
HIV infection (early)	*S. pneumoniae, H. influenzae, Mycobacterium tuberculosis*
HIV infection (late)	The pathogens listed for early infection plus *Pneumocystis jiroveci, Cryptococcus, Histoplasma, Aspergillus,* atypical mycobacteria (especially *Mycobacterium kansasii*), *P. aeruginosa, H. influenza*
Hotel or cruise ship stay in previous 2 weeks	*Legionella* species
In context of bioterrorism	*Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), *Francisella tularensis* (tularemia)
Influenza active in community	Influenza, *S. pneumoniae, Staphylococcus aureus, H. influenzae*
Injection drug use	*S. aureus*, anaerobes, *M. tuberculosis, S. pneumoniae*
Lung abscess	CA-MRSA, oral anaerobes, endemic fungal pneumonia, *M. tuberculosis*, atypical mycobacteria
Neutropenia	*S. pneumoniae,* gram-negative bacilli (especially, *Pseudomonas aeruginosa*)
Nursing home residents*	*S. pneumoniae,* gram-negative bacilli (especially, *Klebsiella pneumoniae*), influenza A or B, *S. aureus,* oral anaerobes, *M. tuberculosis*
Solid organ transplant recipients > 3 months after transplant	*S. pneumonia, H. influenza, Legionella* species, *Pneumocystis jiroveci,* Cytomegalovirus
Structural lung disease (e.g., bronchiectasis)	*Pseudomonas aeruginosa, Burkholderia cepacia, S. aureus*
Travel to or residence in Southeast and East Asia	*Burkholderia pseudomallei,* avian influenza, SARS
Travel to or residence in southwestern United States	*Coccidioides* species, Hantavirus
Young adults (age < 30)	*Streptococcus pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae*

*Pneumonia in nonambulatory residents of nursing homes and other long-term care facilities should be considered a health care–associated pneumonia (HCAP) as described in Chapter 14.

CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; COPD, chronic obstructive pulmonary disease; SARS, severe acute respiratory syndrome.

Adapted from Mandell LA, Wunderink RG, Anzueto A, et al: Infectious Diseases Society of America/ American Thoracic Society consensus guideline on the management of community-acquired pneumonia in adults. Clin Infect Dis 44:S27-S72, 2007.

epithelial cells per low-power field can determine whether the sputum is an adequate sample from the lower respiratory tract. Prior antibiotic therapy decreases the usefulness of sputum cultures, because the chance of isolating an organism from sputum decreases by up to 50% after just one to two doses of antibiotic. Bronchoscopy and bronchoalveolar lavage often increase the yield of Gram stain and culture but are usually reserved for patients who do not respond to initial empirical antibiotics, are critically ill, or may harbor resistant or uncommon organisms.

BLOOD CULTURES AND THORACENTESIS RESULTS

Although positive blood culture results are considered definitive (i.e., highly specific) in establishing the cause of CAP, such results occur in only about 10% of hospitalized patients with CAP (i.e., low sensitivity). Of these, 60% to 70% of cultures grow *S. pneumoniae*. The low prevalence of positive blood cultures partly results from prior administration of antibiotics.

Pleural effusions occur in 10% to 50% of patients with CAP. A diagnostic thoracentesis should be performed if the effusion is large (> 5 cm in height on a lateral upright chest radiograph), the clinical presentation unusual, or the patient fails to respond to initial therapy. Pleural effusions with a pH > 7.3, glucose levels > 60 mg/dL, and lactate dehydrogenase levels < 1000 IU/dL usually resolve with antibiotic therapy alone. If the fluid has gross purulence, pH < 7.20, glucose level < 60 mg/dL, or organisms seen on Gram stain, the patient should undergo chest tube drainage. Of note, one should not send specimens with thick pus to the laboratory for measurement of pH—they plug up the arterial blood gas analyzers, and knowledge of the pH is unnecessary because the gross appearance indicates an empyema.

OTHER DIAGNOSTIC TESTS

Measuring acute and convalescent serologic titers for various atypical respiratory pathogens has no practical role in the management of CAP because the results do not guide therapy. As such, they should not be ordered in the routine patient with CAP.

The presence of a *urine antigen* for *Legionella* is highly sensitive to document infection with *L. pneumophila* (serogroup 1), which causes 70% to 90% of *Legionella* pneumonia cases. The *Legionella urine antigen* does not, however, exclude infection by other serogroups of *L. pneumophila* or other *Legionella* species (which combined cause 10% to 30% of CAP resulting from *Legionella*). None of the other tests available for diagnosing CAP resulting from *Legionella*—such as cultures of sputum or tracheal aspirate, direct fluorescent antibody testing, and acute anti-*Legionella* serum titer—is as sensitive as the urine antigen test. The sensitivity of cultures also declines after the start of anti-*Legionella* antibiotic administration.

Likewise, the Food and Drug Administration (FDA)–approved urinary antigen test for *S. pneumoniae* antigen may be useful in patients with CAP, particularly when antibiotics were started before cultures were obtained, because it is 50% to 80% sensitive and has high (> 90%) specificity (in adults and in the absence of an episode of CAP within 3 months).

A rapid respiratory virus screen (or other tests for influenza, such as molecular probes) can be performed on nasopharyngeal washings, swab, or, less preferably (because of dilution), on bronchoalveolar lavage fluid. This highly sensitive test can confirm a viral cause within 24 hours or sooner with high specificity. Biomarkers of bacterial infection, such as procalcitonin, may help differentiate bacterial CAP from viral etiologies or from noninfectious causes of dyspnea and abnormal chest radiographs, such as congestive heart failure. Furthermore, finding no rise in procalcitonin levels has been demonstrated to be useful in curtailing the duration of antibiotics in cases for which it is initially uncertain if bacterial infection is present.

Risk Factors for Mortality and Complications

It is important to identify patients with severe infection or a high risk of complications from CAP to inform site-of-care decisions. Mortality for CAP varies from < 1% to as high as 60% when patients with CAP are stratified according to number of risk factors that represent severity of disease and host factors as described later. Of those hospitalized for CAP, ~10% are treated in an ICU. Although there is considerable variability among institutions for criteria for ICU admission, one study reported that about half (45%) of patients who were treated in an ICU for CAP were initially admitted to a non-ICU inpatient unit.

Prediction rules, such as the Pneumonia Severity Index (PSI) (pda.ahrq.gov/psicalc.asp) and the British Thoracic Society's CURB-65 (confusion, urea, respiratory rate, and blood pressure in > 65 year olds, available at www.mdcalc.com/curb-65-severity-score-community-acquired-pneumonia), can identify patients with CAP of moderate to high severity for whom hospitalization is recommended. Although lacking prospective validation, the Infectious Disease Society of America–American Thoracic Society (ISDA-ATS) CAP guidelines have proposed criteria for admission to an ICU or high-level monitoring unit if three or more minor criteria or either of the major criteria in Table 65.2 are present.

A meta-analysis of 41 studies established the frequency of common complications of CAP (Table 65.3).

Treatment

ANTIBIOTIC SELECTION

Because one cannot often determine the cause of CAP on admission, initial treatment must be empirical (Table 65.4). If the causative pathogen is identified during the course of therapy,

TABLE 65.2 ■ **IDSA-ATS Criteria for Severe Community-Acquired Pneumonia.**

Minor Criteria* (ICU Admission Is Suggested If Patient Has Three or More Minor Criteria)
Respiratory rate ≥ 30 breaths/min
PaO_2/FiO_2 ratio† ≤ 250
Multilobar infiltrates
Confusion/disorientation‡
Uremia (BUN level, ≥ 20 mg/dL [> 7.1 mmol/L])
Leukopenia§ (WBC count, < 4000 cells/mm^3)
Thrombocytopenia (platelet count ≤ 100,000/mm^3)
Hypothermia (core temperature, < 36° C)
Hypotension requiring aggressive fluid resuscitation
Major Criteria (Absolute Indication for ICU Admission)
Invasive mechanical ventilation
Septic shock with the need for vasopressor

ISDA, Infectious Disease Society of America; ATS, American Thoracic Society; BUN, blood urea nitrogen; PaO_2/FiO_2, arterial oxygen pressure/fraction of inspired oxygen; WBC, white blood cell.

*Other criteria to consider include hypoglycemia (in nondiabetic patients), acute alcoholism/alcohol withdrawal, hyponatremia, unexplained metabolic acidosis or elevated lactate level, cirrhosis, and asplenia.

†A need for non-invasive ventilation can substitute for a respiratory rate ≥ 30 breaths/min or a PaO_2/FiO_2 ratio ≤ 250.

‡New disorientation to person, place, or time.

§As a result of infection alone.

Adapted from Mandell LA, Wunderink RG, Anzueto A, et al: Infectious Diseases Society of America/American Thoracic Society consensus guideline on the management of community-acquired pneumonia in adults. Clin Infect Dis 44:S27-S72, 2007.

one should convert treatment to the most appropriate (narrow spectrum) antibiotic(s). Note that overall, ~20% of *S. pneumoniae* strains in the United States have high-level resistance to penicillin, with some areas having higher rates. Other parts of the world experience penicillin resistance in > 50% of *S. pneumoniae* strains. In addition, these isolates are also frequently resistant to other commonly used antibiotics, such as macrolides. Fortunately, resistance to third- and fourth-generation cephalosporins and respiratory fluoroquinolones is rare. One must *always* consider the current local resistance patterns when making empirical treatment decisions.

TABLE 65.3 ■ **Frequency of Complications of Community-Acquired Pneumonia**

Hepatic abnormalities*	12.3%
Pleural effusion	10.6%
Renal failure	10.4%
Congestive heart failure	8.6%
Respiratory failure	7.8%
Shock	7.7%
Lung abscess	6.3%
Pneumothorax	5.7%
Empyema	5.2%

*Jaundice, liver function test abnormalities, or hepatic failure.

Adapted from Fine MJ, Smith MA, Carson CA, et al: Prognosis and outcomes of patients with community-acquired pneumonia. JAMA 275:134-141, 1996.

TABLE 65.4 ■ **ISDA-ATS 2007 Guidelines: Recommended Antibiotics for Patients in the Intensive Care Unit with Community-Acquired Pneumonia.**

A β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) *plus* either azithromycin (500 mg IV daily) *or* a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg IV daily]) (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended)

Special Concerns

If *Pseudomonas* is a consideration:

—An antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750 mg)

or

—The above β-lactam plus an aminoglycoside and azithromycin

or

—The above β-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for above β-lactam)

If CA-MRSA is a consideration:

—Add vancomycin or linezolid

If patients are known or suspected to be positive for the human immunodeficiency virus:

—Add co-trimoxazole (unless contraindicated) for *Pneumocystis jiroveci* (see Chapter 23)

CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus;* ICU, intensive care unit.

**Adapted from Mandell LA, Wunderink RG, Anzueto A, et al: Infectious Diseases Society of America/American Thoracic Society consensus guideline on the management of community-acquired pneumonia in adults. Clin Infect Dis 44:S27-S72, 2007.*

DURATION OF THERAPY

Although the duration of treatment remains somewhat arbitrary, the usual recommendations are 10 days for common bacterial pneumonias, 10 to 14 days for *M. pneumoniae* and *C. pneumoniae* CAP, and 14 to 21 days for *Legionella* pneumonias (although comparative studies of different duration of treatment for *Legionella* are lacking). Generally, one should convert from intravenous (IV) to oral therapy when the patient is clinically improving, hemodynamically stable, and able to absorb oral medications.

Clinical Course

RESOLUTION

After the initiation of CAP therapy, fever usually resolves in 2 to 4 days (more rapidly with *S. pneumoniae*). White cell elevation resolves after about 4 days. Abnormal clinical findings, however, may persist beyond 7 days in 20% to 40% of patients with *M. pneumoniae* and *C. pneumoniae* (with cough sometimes lasting up to 3 to 4 weeks). Resolution of chest radiograph findings generally lags behind clinical improvement. The radiograph clears completely by 4 weeks in only 60% of otherwise healthy patients younger than 50 years of age. In older patients and those with bacteremia, chronic obstructive pulmonary disease, alcohol abuse, or other chronic illness, the radiograph clears by 4 weeks in only about 25% and may require 12 or more weeks for full resolution.

NONRESOLUTION OR RECURRENCE OF COMMUNITY-ACQUIRED PNEUMONIA

Failure of a CAP to resolve occurs in 6% to 15% of hospitalized patients. This may be due to the nature of the infecting pathogen, the regimen selected for empirical therapy, anatomic factors affecting clearance of infection, or other noninfectious processes that may mimic CAP (Table 65.5).

TABLE 65.5 ■ **Selected Causes of Apparent Empirical Antibiotic Failure**

Anatomic Factor	Endobronchial obstruction
Antibiotic-Related Factors	Altered drug metabolism
	Continued fever caused by antibiotic (drug fever)
	Inadequate dosing
	Inadequate spectrum
	Poor absorption or penetration
Infectious Factors	Empyema or lung abscess
	Resistant organism
	Unsuspected infection elsewhere
	Unusual organism*
Noninfectious Factors	Acute respiratory distress syndrome
	Congestive heart failure
	Malignancy
	Pulmonary hemorrhage
	Recurrent aspiration

**Pneumocystis jiroveci, Mycobacterium tuberculosis*, fungal, viral.

Computed tomography of the chest can provide additional useful information. For example, it may more clearly define the nature of a pulmonary infiltrate or evaluate the presence of a loculated empyema, interstitial disease, cavitation, or adenopathy. Bronchoscopy may help differentiate non-infectious causes of pulmonary infiltrates from CAP or diagnose infections with unusual pathogens in immunocompromised hosts. Rarely, open lung biopsy may be required for definitive diagnosis.

Recurrent pneumonia is defined as the occurrence of two or more episodes of pneumonia separated by at least a 1-month period of radiographic and symptomatic resolution. This is most commonly associated with bronchiectasis, chronic obstructive pulmonary disease, and congestive heart failure, but bronchial obstruction and chronic aspiration must also be considered.

Clinical Pearls

1. Pneumonia is the leading infectious cause of death in the United States.
2. The elderly often lack the classic symptoms of pneumonia.
3. Distinguishing between *typical* versus *atypical* causes of pneumonia based on clinical signs/symptoms is unreliable.
4. *Streptococcus pneumoniae* (pneumococcus) remains the most common cause of CAP.
5. Up to 40% of patients with *Pneumocystis (carinii) jiroveci* pneumonia have normal chest radiographs on presentation.
6. Infection with *Legionella* species other than *L. pneumophila* is more common in the immunosuppressed.
7. Always base empirical treatment decisions on the current local patterns of resistance.

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CHAPTER 66

Necrotizing Fasciitis and Related Soft Tissue Infections

Eugene F. Reilly ■ Vicente H. Gracias

In 1871, Confederate Army surgeon Joseph Jones reviewed more than 2600 cases of "hospital gangrene"—the first published description of necrotizing soft tissue infection (NSTI)—revealing a mortality of 46%. Although better understanding of the pathophysiology of these infections, directed therapy with modern antibiotics, and greater awareness of the disease among clinicians have improved the prognosis of these deep tissue infections, NSTI remains a diagnostic and therapeutic challenge with substantial morbidity and mortality.

Several factors have been implicated in contributing to poor outcomes. Perhaps the most important prognostic indicator is the *time to diagnosis*. Subtle and relatively benign changes of the skin overlying NSTIs commonly belie the magnitude of destruction underneath. The insidious nature of many NSTIs requires great awareness and a high index of suspicion. Potentiating the delay in the diagnosis of NSTI is its rarity. In the United States, NSTI has an incidence of ~1000 cases per year. Thus, most ICU practitioners see only a few cases in their careers—making recognition of NSTI that much more challenging.

Soft Tissue Infections

LAYERS OF SOFT TISSUE

The "soft tissue" is composed of four distinct layers of tissue: the skin, subcutaneous tissue or "superficial fascia," deep fascia, and muscle. Dividing the soft tissue into these four anatomic layers can be helpful both descriptively and therapeutically. Infectious processes that affect the two most superficial layers are usually self-limited and can be treated effectively with nonsurgical therapy—that is, local hygiene and antibiotics. Infections of the deep fascia and muscle, which can spread rapidly and produce large areas of tissue destruction culminating in multiorgan dysfunction, virtually always require surgical therapy.

The *skin* is a two-layer membrane consisting of the epidermis and dermis. These layers are tightly fused above the subcutaneous tissue. When intact, the skin presents an almost impenetrable barrier to microorganisms. However, skin damaged by trauma or disease does not provide nearly as effective a defense. The blood supply of the skin runs horizontally at the junction of the dermis and subcutaneous tissue (Figure 66.1), and it is crucial for maintaining the skin's integrity.

The *subcutaneous tissue or superficial fascia*, located between the dermis and deep fascia,consists of fat and loose connective tissue. Most soft tissue infections occur at this level and are commonly termed *cellulitis* or *adipositis*. The subcutaneous tissue is only loosely fixed to the deep fascia. This junction between superficial fascia and deep fascia is a potential space, called the *fascial cleft*. Infection can spread rapidly in this plane, impeded only where the superficial fascia is adherent to bone.

The *deep fascia* is a layer of strong connective tissue that overlies and separates major muscle groups. Where present, the deep fascia effectively deters the spread of infection from the

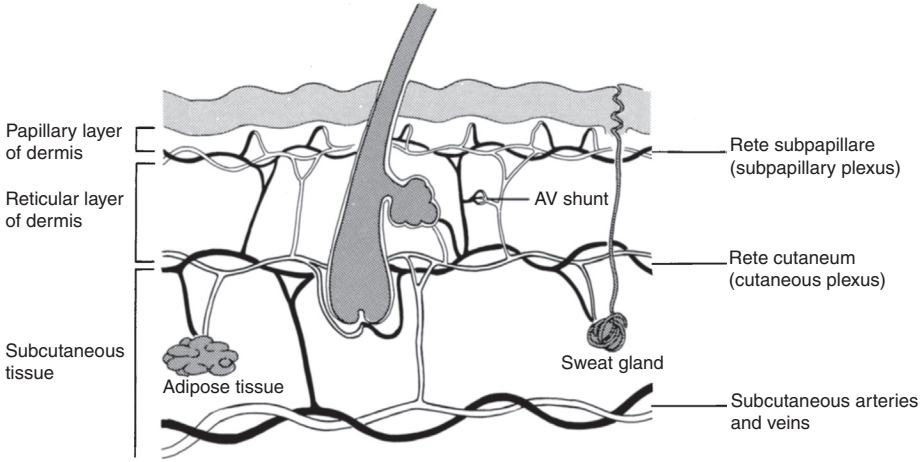


Figure 66.1 The dermal vasculature consists of superficial and deep plexuses that are connected by numerous communicating vessels. This rich blood supply is responsible for the skin being spared until relatively late in cases of necrotizing fasciitis, despite the infection-induced thromboses occurring in the vessels of the subcutaneous tissue. *(From Cormack DH, Ham AW, Ham's Histology, 9th ed. Philadelphia: J.B. Lippincott, 1987, p 467.)*

superficial fascia into the muscle. Infection that extends to this layer and spreads within the fascial cleft is often termed *fasciitis*. Where the deep fascia is absent, for example, in the face and scalp, superficial infections can quickly spread into deeper tissues.

Skeletal muscle is the deepest layer of soft tissue and is made up of long multinucleated cells enclosed in the sarcolemma. Multiple cells are held together by a fibrous epimysium in which nerves and blood vessels run. The blood supply is extensive, with each muscle fiber receiving blood from several capillary beds. The richness of this blood supply is, in part, responsible for muscle's high resistance to infection. When infection occurs at this level, it may be called *myositis* or *myonecrosis*.

PATHOGENESIS

Although soft tissue infections can originate from defects in systemic defenses, they more commonly develop as a result of local damage to the corneal layer of the epidermis, allowing microorganisms to invade. Alternatively, NSTIs sometimes originate from underneath the skin by way of a perforated viscus—notably the colon, rectum, or anus. Epidermal damage leading to NSTI can be caused by trauma as subtle as that associated with tape removal, hair plucking, or occlusive dressings that retain water and macerate the skin.

Like the epidermis, normal soft tissue is resistant to infection. Other factors influencing the development of NSTI include the size of the bacterial inoculum, local host defenses, tissue perfusion, and adjacent tissue trauma.

Another factor leading to the severity of some NSTIs is the contribution of exotoxins from some of the causative organisms. Clostridial infections are complicated by α-toxin, which causes tissue destruction and hemodynamic instability. Infections by *Staphylococcus aureus* and streptococcal species are complicated by a plethora of toxins. M-surface proteins enhance the bacteria's tissue adherence and ability to evade host defenses. Exotoxins A and B cause capillary leakage and impaired blood flow. Streptolysin O and superantigen lead to a hyperinflammatory response resulting in severe sepsis or septic shock, which is often unrecoverable.

Thrombosis of deep blood vessels of the affected area is a hallmark of NSTI. However, the skin is able to receive its blood flow largely from the skin around it via the horizontal vascular plexus in the deep dermis (see Figure 66.1), rather than from the tissue beneath, leading to the NSTI's often underwhelming external appearance.

MICROBIOLOGY

Necrotizing soft tissue infections may by caused by a variety of organisms, and in many combinations. Historically, clostridia are often cited as the causative organism of necrotizing fasciitis (for example, in "gas gangrene" described in trench warfare). Although clostridial soft tissue infections still exist today, they are uncommon. Two microbial subtypes of NSTI are usually described, with the addition by some authors of a third.

Type I infections are polymicrobial and are the most common form; they are commonly found on the trunk and perineum. An average of four different organisms may be cultured from such wounds and usually include a combination of gram-positive cocci, gram-negative rods, and anaerobes. Both bacteroides and clostridia may be present. *Clostridium septicum* is a rare finding, but when present it is highly suggestive of a perforated colon cancer. Type I infections tend to occur in immunocompromised patients.

Type II infections are caused by a single organism, usually *Streptococcus pyogenes* (i.e., group A streptococcus), occasionally in association with *Staphylococcus aureus*, and are commonly found on the extremities, though systemic toxic shock syndrome can result. In addition, community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) has become more common, especially in intravenous (IV) drug users; MRSA may now be isolated in 40% of necrotic wounds. These infections tend to occur in otherwise healthy, young patients.

A *type III* infection has been described and includes the small subset of NSTIs caused by *Vibrio vulnificus*. This bacterium is encountered when open wounds are exposed to warm seawater, though necrotizing soft tissue infection by this mechanism is unusual. Type III NSTI is remarkable for its rapid progression to multisystem organ failure and death within 24 hours.

Clinical Manifestations and Differential Diagnosis

SKIN INFECTIONS

Most infections confined to the skin are caused by streptococcal and staphylococcal infections. Examples of these types of infections, nonspecifically called pyodermias, include impetigo, ecthyma, and erysipelas (Table 66.1).

Impetigo consists of two forms, a bullous form caused by *S. aureus* and an epidemic form caused by group A *Streptococcus pyogenes*. Impetigo begins as a small red papule, progresses to a vesicle, and eventually ruptures, leaving its hallmark ulcer with a yellow crust. Untreated, the ulcer may last for months, but cellulitis and lymphangitis are rare. Glomerulonephritis is a feared complication of the streptococcal variant, and epidemic nephritis has been described after outbreaks of impetigo. Prompt treatment with penicillin reduces the risk of nephritis.

Ecthyma is essentially a deeper form of impetigo. It also begins as a vesicle but produces a large "punched out" ulcer with a violaceous border and a thick eschar. Although superficial pseudomonal pyoderma in the immunocompromised patient can present with lesions that are similar to both impetigo and ecthyma, lesions from ecthyma can usually be differentiated by their blue-green exudate and fruity odor. Embolic pustular lesions in patients with systemic *Pseudomonas aeruginosa* and *S. aureus* also present with ulcers similar to impetigo. These ulcers can usually be differentiated from impetigo, however, by their more purulent appearance in addition to the clinical setting in which they present.

TABLE 66.1 ■ **Soft Tissue Layers and Infections**

Layer Involved	Infection	Causative Bacteria and Comments
Skin	Impetigo	*Staphylococcus* (bullous form) Group A *Streptococcus pyogenes* (epidemic form)
Skin	Ecthyma	Deeper form of impetigo
Skin	Erysipelas	*S. pyogenes*; has distinct violaceous border
Skin	Pyoderma	*Pseudomonas aeruginosa*; typically in immunocompromised hosts; "pyoderma gangrenosa" is a blue-red ulcer surrounding a necrotic base
Skin	Embolic ulcers	*P. aeruginosa* and *S. aureus*
Superficial fascia (Subcutaneous tissue)	Cellulitis	*S. pyogenes*, usually without preceding trauma; gram-negative bacilli and anaerobes occur with cellulitis resulting from bowel perforations or animal/human bites (see text)
Fascial cleft and deep fascia	Necrotizing fasciitis	Clostridial species; mixed aerobes-anaerobes; *Vibrio* species, *S. pyogenes*
Muscle	Myonecrosis	Clostridial species and other mixed aerobes-anaerobes can produce subcutaneous gas; group A beta-hemolytic *S. pyogenes* (so-called flesh-eating bacteria) causes necrotizing fasciitis with myonecrosis
	Abscess	*S. aureus*; associated with less pain or systemic toxicity; usually occurs after trauma

Erysipelas is a painful and indurated lesion with a sharply circumscribed border, commonly associated with fever and leukocytosis. This type of infection is always confined to the skin, but if left untreated it can progress to cellulitis or even necrotizing fasciitis. *S. pyogenes* is almost always the cause.

SUPERFICIAL FASCIAL INFECTIONS

Infections of the superficial fascia without necrosis or suppuration are commonly referred to as *cellulitis*. Localized tenderness, heat, erythema, and swelling usually accompany systemic symptoms, such as malaise, fever, and chills. Obvious signs of skin trauma may be absent. Cellulitis can be differentiated from a more superficial erysipeloid type of infection by the absence of a distinct indurated border. Clinically, the difference means little because the therapy for both is intravenous antibiotics. The most common inciting organism is *S. pyogenes,* and the infection is usually secondary to minor skin trauma.

Mixed gram-negative cellulitis is characteristically seen as a result of a disruption in bowel mucosa or infected bite wounds. When the bowel is the source of infection, organisms include *Escherichia coli*, *Klebsiella, Enterobacter, Serratia,* and *Bacteroides* species. Human bites are often accompanied by *Eikenella corrodens* infection, whereas dog and cat bites may be complicated by *Pasteurella multocida* infections. Both these latter gram-negative bacilli are sensitive to penicillin.

FASCIAL CLEFT AND DEEP FASCIAL INFECTIONS

Once infecting organisms reach the potential space between the subcutaneous tissue and the deep fascia, the fascial cleft, they are free to spread horizontally along this potential space. In doing so, they produce a rapidly progressive and destructive infective process. This is the dreaded entity

commonly referred to as *necrotizing fasciitis.* Once the infection of this space is established, the disease may present in one of two ways.

First, it can present as a rapidly progressive fulminant infection, with the skin developing large bullae containing black fluid filled with bacteria. Without therapy, these lesions progress to full-thickness burn-like eschars and lead to progressive shock and eventual death. Despite its sudden onset and rapidly fulminant course, NSTIs that present in this fashion are often easier to diagnose early and manage because of the physical exam findings.

Second, and more commonly, NSTI may present in a more subtle fashion with little superficial evidence of the underlying progressive spread of tissue destruction. The only clinical signs may be a faint line of erythema at the leading edge of the infection and thin "dishwater" drainage emanating from the lesion. Pain may be out of proportion to the physical findings, or paresthesia may be present because of destruction of subcutaneous nerves.

In both types of presentations, the underlying muscle is usually not affected, but most of the subcutaneous tissue from the deep fascia outward is devitalized by rapidly progressing sepsis-induced vascular thrombosis. Crepitus secondary to gas production may extend widely beyond the areas of obvious infection. Gas production is commonly ascribed to clostridial infections; however, other mixed synergistic aerobic and anaerobic infections may also produce gas, albeit to a lesser extent.

Fournier disease, first reported in 1883, is a necrotizing fasciitis of the scrotum and surrounding perineum, penis, and abdominal wall. The most common causes are local trauma, periurethral extravasation of infected urine, or perirectal abscess. Because the subcutaneous tissue is sparse, the scrotal skin is directly applied to the fascia, and fasciitis in this area tends to spread rapidly and involve the skin early in the course. For this reason, diagnosis is usually made quickly and, as a result, the prognosis is somewhat better than that for necrotizing fasciitis in other locations.

MUSCLE INFECTIONS

Deep muscle infections can be difficult to diagnose initially because they are often obscured by overlying normal skin and subcutaneous fat. These infections range in severity from a relatively benign staphylococcal abscess to life-threatening clostridial or *S. pyogenes* myonecrosis. Staphylococcal and clostridial infections are usually caused by trauma. Clostridial infections are more explosive at onset with a shorter incubation time (< 24 hours). They usually present with excruciating pain, extensive gas production, a sweet but foul odor, and rapidly progressive systemic toxicity. Staphylococcal abscesses are more indolent (incubation over 3 to 4 days), pain and gas production are much less pronounced, the odor is often more pungent than sweet, and systemic toxicity is much more limited. *S. pyogenes* myonecrosis is virtually always accompanied by necrotizing fasciitis and severe systemic toxicity.

Diagnosis and Management

APPROACH TO DIAGNOSIS

Patients with NSTI classically present with complaints of pain, anxiety, and diaphoresis of acute onset. Though breaks in the skin are often the cause of the infection, only 10% to 40% of patients will relate this history.

The depth of a soft tissue infection may be directly proportional to the severity of disease, but it is often inversely proportional to its external manifestations. Although many authors stress shock, fever, and systemic illness in the description of NSTI, most patients present with localized erythema, tenderness, and edema as the only signs of infection. Crepitus from subcutaneous emphysema is present in only 10% to 31% of patients. In a small subset of patients with rapid,

fulminant disease, cardiovascular collapse can occur even before the onset of any severe skin or soft tissue changes.

There is an inverse relationship between the depth of infection and its appearance on physical exam, but even simple superficial infections—which may appear beefy red, hot, and painful—if treated inadequately or in an untimely fashion, can progress to deeper, more life-threatening infections, which require prompt surgical debridement.

Retrospective studies suggest that mortality is significantly increased if surgery is delayed more than 24 hours (6% versus 25%). Overreliance on negative diagnostic test results (fine-needle aspiration and negative plain films), equivocal physical findings, and admission to a nonsurgical service have been implicated as factors leading to diagnostic and therapeutic delays.

Fine-needle biopsies and plain film radiographs are somewhat specific, but they are not at all sensitive for ruling out deep necrotizing infections. Ultrasound may be useful for detecting fluid collections or abscesses, but it is generally not helpful otherwise and its use in diagnosing NSTI is discouraged. Computed tomography (CT) has an overall sensitivity for NSTI of ~80% and is much more sensitive for subcutaneous emphysema than plain radiographs, but not all necrotizing infections produce gas. The utility of IV contrast is not clear. Magnetic resonance imaging (MRI) may offer a diagnostic advantage by its capacity to delineate fascial planes well and has a sensitivity of 90% to 100%, but it is nonspecific (50% to 85%), time consuming, and not always readily available.

The gold standard for diagnosis is operative exploration. Typical findings include malodorous or grayish discharge, frank necrosis and associated venous thrombosis, and loss of the usual tissue integrity with blunt dissection. Deep-tissue cultures are usually not necessary and more superficial cultures may be misleading. If a tissue biopsy is performed, it is most useful to include a margin of healthy tissue with the specimen for review by an experienced pathologist.

TREATMENT

Prompt debridement remains the most important modality for both diagnosis and treatment of NSTI. Antibiotics are an important adjunct to stem the tide of local spread and systemic sepsis; however, local ischemia within the grossly infected tissue limits their usefulness as a primary therapy.

The surgical field should be extended in all directions to healthy, bleeding tissue regardless of the size of the resulting tissue defect. It is common to require multiple procedures separated by 12 to 24 hours to achieve this goal, and the boundaries of the excision frequently must be extended far beyond what was anticipated preoperatively. Amputation of an affected extremity must be considered if the area of necrosis includes a joint or if the infection is progressing rapidly toward the torso. Limb amputation is necessary in as many as 20% of NSTI, particularly among IV drug users. Fournier disease in the perineum may require fecal diversion through a temporary colostomy to achieve source control and to make the local environment amenable to healing. That said, surgical castration is rarely necessary. It is not clear that one type of postoperative dressing is superior to another, but many large defects require either skin grafting or myocutaneous flaps for proper coverage once the infection has been controlled.

Parenteral antibiotics should be started promptly when there is any suspicion of NSTI, and they should not be withheld while the workup is ongoing (Figure 66.2). If symptoms do not improve in 12 hours, or if they worsen, surgical exploration is indicated. Parenteral antibiotics should be given that are effective against known or suspected pathogenic bacteria (see Table 66.1). For example, for Fournier disease, appropriate coverage includes agents active against *Staphylococcus, Streptococcus,* enterococci, anaerobes, and gram-negative aerobic bacilli. In addition, some clinicians advocate coverage of *S. pyogenes* necrotizing fasciitis with both penicillin (for bacteria in the growth phase) and clindamycin (for bacteria in the stationary phase). Antibiotic selection should be guided by local sensitivity patterns of likely organisms if available.

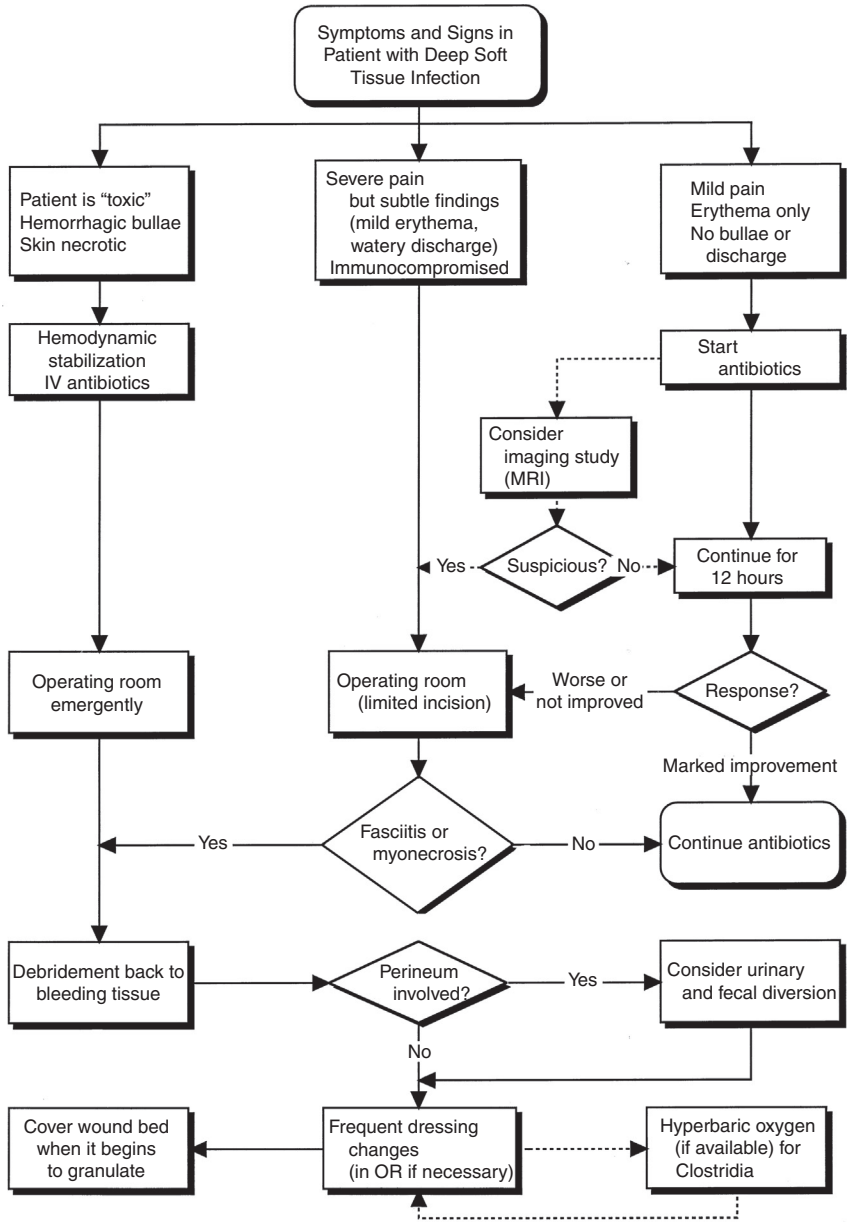


Figure 66.2 Diagnostic and therapeutic algorithm for management of deep soft tissue infections.

Intravenous immune globulin (IVIG) may have a role in streptococcal and staphylococcal infection, by binding toxins and thereby limiting the inflammatory response. This treatment modality has gained favor in some centers, but it is not Food and Drug Administration (FDA) approved, poorly studied, expensive, and has no standard dosing regimen.

Hyperbaric oxygen (HBO) therapy is used in some centers as an adjunct to more conventional therapy. On 100% oxygen, if the chamber pressure is raised from one atmosphere (equal to

room air at sea level) to the two to three atmospheres used in most hyperbaric oxygen regimens, the oxygen tension in soft tissues increases from 75 mm Hg to 300 mm Hg. Theoretically, this supranormal tissue oxygen tension should inhibit infection by anaerobic organisms and augment the leukocytes' oxidative killing effect. In practice, studies have not conclusively demonstrated any reduction in morbidity or mortality. If there is any benefit at all, it is probably greatest in infections caused by anaerobic species and likely to be modest. HBO should be an adjunctive therapy only and, like IVIG, should not be viewed as a substitute for prompt, thorough debridement and broad-spectrum parenteral antibiotics.

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CHAPTER 67

Acute Neuromuscular Weakness

Neil M. Masangkay ■ Shawn J. Bird

The development of acute neuromuscular weakness is one of the more common neurologic syndromes requiring admission to the intensive care unit (ICU). Because respiratory muscle weakness is associated with these disorders, hypercapnic respiratory failure is a frequent complication. Furthermore, bulbar weakness can lead to difficulty swallowing and weakened cough, increasing the risk of aspiration.

General Approach to Acute Neuromuscular Weakness

MONITORING FOR RESPIRATORY COMPROMISE

In the setting of neuromuscular disorders, careful respiratory monitoring should be the first priority in the care of these patients. The same general approach to respiratory failure applies to all neuromuscular disorders. Although oxygenation should be monitored closely in these patients, pulse oximetry and arterial blood gases (ABGs) cannot be relied on to gauge acute respiratory muscle weakness. This is because abnormalities in these measures frequently lag behind respiratory muscle fatigue or weakness that will imminently result in respiratory failure. Vital capacity (VC) and maximal inspiratory pressure (MIP) are more useful in these patients. The vital capacity reflects the mechanical strength of the muscles of respiration and can be easily performed at the bedside. Maximal inspiratory pressure provides similar information and, like the vital capacity, can be checked frequently at the bedside. For patients with acute neuromuscular weakness, the VC, MIP, or both should be repeated at frequent intervals. How frequently these parameters should be measured depends on the disease and the rate of progression of weakness; for example, every 2 hours may be desirable in a patient with a rapidly worsening myasthenic crisis.

In some patients it is difficult to accurately assess the VC or MIP because of facial weakness (poor seal with the mask) or delirium. Thus, these measures may be falsely low. The VC and MIP should always be interpreted in the context of the clinical signs of respiratory muscle weakness (such as increasing respiratory rate, tachycardia, use of accessory muscles of respiration, and paradoxical motion of the diaphragm), as well as the trend in these measures.

NEED FOR VENTILATORY SUPPORT

In the setting of worsening respiratory weakness or clinical concern about the patient's ability to protect their airway, the clinician should be aggressive about elective intubation. With close monitoring, endotracheal intubation should be performed as an elective procedure before precipitous respiratory collapse (i.e., not in response to this complication). As long as the patient does not need an artificial airway to clear secretions or prevent airway occlusion, noninvasive ventilation may serve as a useful temporizing modality to provide assisted ventilation, particularly if the respiratory muscle weakness can be reversed quickly (see Chapter 3), but concern for aspiration is an important consideration in this scenario.

BOX 67.1 ■ Guidelines for Starting Assisted Ventilation* for Patients with Acute Neuromuscular Weakness

Ventilatory Ability (Vital Capacity [VC] and Maximal Inspiratory Pressure [MIP])*†

VC < 20 mL/kg predicted body weight (PBW‡), *or*
VC falling toward 20 mL/kg PBW with signs of respiratory distress or paradoxical respirations, *or*
MIP worse (i.e., less negative) than −30 cm H_2O

Airway Integrity

Inability to clear oral secretions *or* intermittent aspiration *or*
Obstruction of airway in certain positions

Oxygenation

Same as with other medical conditions

**Consider use of non invasive ventilation in patients who do not need an artificial airway to clear secretions. Note: Negative inspiratory force (NIF) is another name for MIP.*
†Best assessed with serial measures that show both the absolute values and the trend.
‡PBW for males = 50 + 2.3 (height [inches] −60); PBW for females = 45.5 + 2.3 (height [inches] −60).

The following parameters warn of impending respiratory arrest and, generally, are indications for intubation (Box 67.1): vital capacity (VC) less than 20 mL/kg predicted body weight (PBW) (see footnote of Box 67.1 for formulas to calculate PBW); VC falling toward 20 mL/kg PBW plus clinical signs of respiratory muscle fatigue, such as increasing respiratory rate, tachycardia, use of accessory muscles of respiration, and paradoxical motion of the diaphragm ("respiratory paradox"); maximal inspiratory pressure (MIP) worse (i.e., less negative) than −30 cm H_2O; or maximal expiratory pressure < 40 cm H_2O. This general guide has been termed by some the "20-30-40 rule." Oropharyngeal weakness with an inability to handle secretions and risk of aspiration or airway obstruction also may necessitate intubation.

DIFFERENTIAL DIAGNOSIS

In evaluating a patient with acutely worsening neuromuscular weakness, it is important to determine if the patient has a known history of neuromuscular disease, such as myasthenia gravis or amyotrophic lateral sclerosis (ALS). Neuromuscular respiratory failure may be part of the natural history of the disease or may be precipitated by transiently increased weakness resulting from an underlying infection, such as a urinary tract infection or pneumonia. Infectious or metabolic disorders should be thoroughly investigated and treated, if found.

Disorders that produce neuromuscular weakness severe enough to result in ICU care, such as myasthenia gravis or the Guillain-Barré syndrome, are generally separated from disorders that develop de novo in the ICU setting (the latter are discussed in Chapter 48).

Not infrequently, the cause of the neuromuscular weakness that results in ICU care is unknown. This necessitates a diagnostic workup because pharmacologic and other interventions vary according to specific causes. In the differential diagnosis of acute neuromuscular weakness, certain clues from the history and examination can help to identify its cause (Table 67.1).

Electrophysiologic studies (nerve conduction studies and needle electromyography, which are collectively called electromyography [EMG]) are usually required to fully investigate these disorders. This is particularly true in individuals with an abnormal mental status (common in the ICU setting) who may not be able to cooperate with a motor and sensory examination. EMG allows full investigation of the presence and nature of peripheral motor and sensory involvement.

TABLE 67.1 ■ **Differential Diagnosis of Acute Neuromuscular Weakness Necessitating ICU Care**[§]

Cause by Localization	Suggestive Clinical Features	Important Diagnostic Tests
Spinal Cord	Sensory level; early urinary symptoms; Babinski signs (present in only ~50% early); spares cranial muscles; weakness may be limited to the legs with thoracic cord lesions	
Acute epidural compression (disc herniation, abscess, tumor, or hemorrhage)	Local neck or radicular pain; history of infection, trauma, or tumor	Spine MRI (or rarely myelogram)
Other causes (transverse myelitis, cord hemorrhage or infarction)	History of trauma or bleeding risk (hemorrhage)	Spine MRI; LP
Anterior Horn Cell (Motor Neuron)	Weakness, without sensory or reflex loss	
Poliomyelitis syndrome (e.g., West Nile virus)	Antecedent systemic viral illness (especially fever and headache)	LP
Paralytic rabies	History of animal bite	FAT and cultures of saliva, serum, and CSF
Multiple Radiculopathies		
Carcinomatous or lymphomatous meningitis	History of carcinoma or lymphoma[*]	LP with cytologic studies
Peripheral Neuropathy	Weakness, with sensory and reflex loss	
Guillain-Barré syndrome[†]	Early loss of reflexes; facial weakness (see text)	LP; EMG
Acute intermittent porphyria[‡]	Associated gastrointestinal or psychiatric manifestations; may be precipitated by new medication	Urine assay for porphyrins
Vasculitic polyneuropathy[‡]	Mononeuropathy multiplex; other organ involvement; history of connective tissue disease	Serologic studies; nerve and muscle biopsy
Acute intoxication (arsenic or thallium or diethylene glycol)[‡]	Illness with nausea, vomiting, and hypotension 2 to 3 weeks prior to neuropathy onset	Serum arsenic or thallium
	Shorter duration of prodrome for diethylene glycol with acute oliguric renal failure	
Neuromuscular Junction	Weakness, without sensory or reflex loss	
Myasthenia gravis	Dysphagia, dysarthria, ptosis, diplopia (see text)	EMG with RNS; AChR and MuSK antibodies
Botulism	History of canned or spoiled food ingestion, or wounds from IV drug use; pupillary unreactivity; descending paralysis	EMG with RNS
Hypermagnesemia	History of renal failure and magnesium supplementation	Serum magnesium
Organophosphate toxicity	History of exposure to pesticides; confusion with muscarinic signs (lacrimation, bradycardia, bronchospasm)	EMG with RNS
Tick paralysis	History of specific tick exposure	Discovery of the attached tick on the patient

Continued on following page

TABLE 67.1 ■ **Differential Diagnosis of Acute Neuromuscular Weakness Necessitating ICU Care§** (Continued)

Cause by Localization	Suggestive Clinical Features	Important Diagnostic Tests
Myopathy	Weakness, without sensory or reflex loss	
Hypokalemic myopathy	History of ↓ K^+, diuretic use, or RTA	Serum K^+
Severe rhabdomyolysis	Muscle pain, myoglobinuria	Serum CK

*Neurologic disorder often the presenting feature.
†Demyelinating neuropathy.
‡Axonal neuropathy.
§These are causes of acute neuromuscular weakness in patients who were previously well neurologically. There are many other causes of chronic neuromuscular weakness that are not listed above (e.g., ALS or muscular dystrophies) that can transiently worsen due to another illness (such as infection).
LP, lumbar puncture; FAT, fluorescent antibody test; EMG, nerve conduction studies and needle electromyography; RNS, repetitive nerve stimulation studies; NMBAs, neuromuscular blocking agents; RTA, renal tubular acidosis; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; AChR, acetylcholine receptor; MuSK, muscle-specific kinase; CK, creatine kinase; ALS, amyotrophic lateral sclerosis.

It can distinguish among disorders of nerve, muscle, and neuromuscular junction. It also provides prognostic information by quantifying the extent of nerve or muscle injury.

Nerve and muscle biopsy are invasive and are not generally performed in the ICU setting, unless there is suspicion of another disorder that is only identified pathologically. Of the few indications for performing a nerve biopsy, suspected vasculitis is the most common. Muscle biopsy should likewise be reserved for patients in whom a specific cause is likely to be identified only by biopsy, such as an inflammatory myopathy (myositis).

The Guillain-Barré Syndrome

The Guillain-Barré syndrome (GBS) is the most common cause of acute flaccid quadriparesis in the United States. This disorder is an acute, inflammatory demyelinating polyneuropathy that is primarily characterized by progressive limb weakness and areflexia. In two thirds of those affected, it occurs 2 to 4 weeks after a viral-like respiratory or gastrointestinal illness. Less commonly, it follows identifiable acute infections, including *Mycoplasma, Campylobacter jejuni,* and viruses (cytomegalovirus [CMV], Epstein-Barr virus [EBV], herpes simplex virus [HSV], and human immunodeficiency virus [HIV]). GBS also rarely follows surgery or certain immunizations. Recognition of this disorder is important because early detection of respiratory failure may limit complications and early therapy may limit nerve fiber loss and the extent of ultimate disability.

The pathogenesis of GBS involves an autoimmune attack on the myelin of peripheral and cranial nerves, which results in an acute segmental demyelination. Because of the demyelination, saltatory conduction (in which the action potential is conducted from one node of Ranvier to the next) across the peripheral nerves is reduced, leading to peripheral nerve symptoms with general preservation of the actual axons. However, axons will be affected by the autoimmune attack to a degree; the level of this "bystander" phenomenon is the most important factor in potential clinical recovery.

CLINICAL PRESENTATION AND SYMPTOMATIC MANAGEMENT

The clinical presentation of GBS usually consists of distal limb numbness and paresthesias, followed by progressive ascending limb weakness. The pace of progression can vary dramatically,

from rapid (complete quadriparesis and intubation over 24 to 48 hours) to slow (progression over 3 or 4 weeks). In addition, respiratory decline may not always parallel the degree of limb weakness and must be followed carefully.

On examination, motor findings are usually more prominent than sensory findings, although sensory symptoms such as paresthesia and pain are common. Facial weakness is present in more than half of patients with GBS. Dysphagia is also common, but extraocular movements are involved in only ~15% of patients. In ~10% of patients, the weakness may begin in the arms and descend into the legs, or respiratory and bulbar involvement may occur early. Deep tendon reflexes are reduced or absent, particularly in weak limbs. Easily elicited reflexes in a weak limb should cast doubt on the diagnosis of GBS. Respiratory muscle weakness can lead to respiratory failure in 15% to 30% of patients.

Autonomic dysfunction is a common complication of GBS and can occur in up to 70% of patients. Sinus tachycardia and hypertension, the most commonly encountered forms of dysautonomia, usually require no treatment. Labile blood pressure with hypertension should be treated with caution, because hypertension in this setting is mostly paroxysmal and treatment may result in periods of marked *hypotension.* Orthostatic hypotension usually responds to intravascular volume expansion. Electrocardiographic changes with ST-T segment and T-wave abnormalities may be seen, and an occasional patient experiences heart block requiring pacemaker placement. Patients can occasionally experience adynamic ileus and urinary retention. Although most of these changes are temporary, close monitoring of blood pressure, fluid status, and cardiac rhythm is essential.

Neuropathic pain is a common problem early in the course of GBS. The pain is often deep and achy and involves the truncal musculature, extending into the limbs. It probably reflects inflammatory disease in the nerve roots. This pain can be severe and occasionally is the overwhelming symptom at presentation. It should be treated aggressively because it often resolves over days to weeks. Narcotics can be used effectively but require close monitoring for adverse effects in the setting of autonomic dysfunction and possible respiratory compromise. Later in the course of disease, patients may experience neuropathic pain of a different sort related to the underlying nerve injury. This pain is usually burning, dysesthetic pain akin to that seen in patients with diabetic neuropathy and may be treated effectively with gabapentin, tricyclic antidepressants, or other agents.

DIAGNOSTIC APPROACH TO SUSPECTED GBS

GBS is primarily a clinical diagnosis that can be made in the presence of an acutely developing quadriparesis with sensory symptoms and hyporeflexia. Laboratory studies, specifically electrophysiologic (EMG) studies and cerebrospinal fluid (CSF) testing, can be obtained to confirm the diagnosis. However, the characteristic abnormalities on the results of these studies (discussed later) often lag behind the onset of disease by up to a week. For this reason, treatment for presumed GBS and the search for alternative diagnoses should not be delayed while waiting for diagnostic confirmation by EMG and CSF studies.

Laboratory studies that may help confirm the diagnosis of GBS are the cerebrospinal fluid (CSF) studies and electrophysiologic tests (EMG). In the examination of CSF, an entity known as "albuminocytologic dissociation" is classically associated with GBS. This involves the elevation of CSF protein, while only a few white blood cells are present in the same CSF sample. The CSF protein is elevated infrequently in the first 48 hours, but most patients with GBS demonstrate this abnormality 7 to 10 days into the illness. There are usually only a few cells in the spinal fluid. If there are more cells present (particularly > 50 white blood cells/μL), GBS associated with HIV seropositivity or, less commonly, carcinomatous meningitis or Lyme disease should be considered. All patients with GBS, but especially those with a CSF pleocytosis or with risk factors for HIV, should have serum tested for HIV seropositivity as well as for HIV viral load since HIV-associated GBS may occur at onset of HIV infection. Nerve conduction studies play the primary role in

identifying specific features of demyelination that are characteristic of GBS. As with CSF analysis, however, these specific features of demyelination are often not seen within the first several days of the illness but appear in most patients after 1 week.

Disorders that can mimic GBS should always be considered. The most important one is *acute cervical spinal cord compression*. Nearly half of patients with acute cervical myelopathy present with reduced reflexes and tone, as part of a spinal injury syndrome (see Chapter 101). The expected features of spasticity and hyperreflexia develop later. Epidural spinal cord compression resulting from tumor, abscess, or hematoma is important to recognize because it may be treatable by emergency decompression. One must suspect this entity on clinical grounds. Important clues to this diagnosis include absence of facial weakness in the setting of profound limb weakness, a level of sensory loss on the trunk (Figure 101.1), and prominent urinary incontinence. When in doubt, spinal cord imaging is necessary. Other acute causes of severe neuropathy are uncommon (see Table 67.1). If the possibility of acute axonal neuropathy secondary to vasculitis is a consideration, biopsy of nerve, muscle, or both may be indicated. Otherwise, biopsy is rarely helpful in the setting of GBS.

TREATMENT OF GBS

Treatment of GBS includes the medical management of the respiratory failure (see Chapters 1, 2, and 3), autonomic abnormalities, and neuropathic pain (see the symptomatic treatment discussed earlier), as well as specific immunotherapeutic interventions. The mainstays of treatment of GBS are plasma exchange (PE, or plasmapheresis) and intravenous immune globulin (IVIG) (Table 67.2). Currently most patients with GBS undergo a course of PE or IVIG. The choice of treatment modalities depends on the individual patient's clinical situation, the local availability of each therapy, and specific clinical factors such as the side effect profile.

Both PE and IVIG have been established as effective in treating GBS in large randomized controlled trials, without an apparent treatment benefit of one over the other. The combination of these two modalities (PE followed by IVIG) has not been shown to be more effective than either one

TABLE 67.2 ■ **Plasma Exchange and Intravenous Immunoglobulin in Treatment of the Guillain-Barré Syndrome and Myasthenia Gravis**

	Plasma Exchange (PE)	Intravenous Immunoglobulin (IVIG)
Major limitations	Frequently requires central access	Periodic shortages of IVIG
	Temporary effect in MG	Temporary effect in MG
	Availability*	
Contraindications	Hemodynamically unstable patient; coagulation disorders	Severe IgA deficiency; previous anaphylaxis to IVIG; renal failure; severe CHF
Adverse reactions	Common: hypotension, transient coagulopathy (caused by the loss of clotting factors)	Common: headache, chills, flu-like symptoms; fluid overload
	Less common: cardiac arrhythmias	Less common: rash, aseptic meningitis
	Serious: catheter-related (sepsis, pneumothorax during insertion)	Serious: acute renal tubular necrosis (usually reversible), thromboembolic events (DVT, PE, MI, stroke)
Standard treatment	PE of 250 mL/kg total plasma volume over 4–6 exchanges over 8–10 days	IVIG 400 mg/kg/day for 5 days

*Should be available in all tertiary centers.
MG, myasthenia gravis; CHF, congestive heart failure; IVIG, intravenous immunoglobulin; PE, plasma exchange, DVT, deep vein thrombosis; PE, pulmonary embolus; MI, myocardial infarction.

alone. Other immunosuppressive agents, including corticosteroids, have not been demonstrated to be efficacious and are not recommended.

IVIG or PE should be started as soon as possible in those unable to walk unassisted or those with respiratory involvement because irreversible nerve loss may occur with delays. Early relapse is seen following PE or IVIG in ~10% of patients and is clustered in the month after the first treatment. If this occurs, further improvement will be seen after additional IVIG or PE treatments.

Myasthenia Gravis

Myasthenia gravis (MG) is a chronic autoimmune disease in which antibodies that are directed against skeletal muscle acetylcholine receptors (AChR) interfere with neuromuscular transmission and produce weakness. Affected patients typically describe a fluctuating course of weakness, without sensory involvement, which can involve the limbs, neck, face, speech and swallowing (bulbar), breathing, and eye movements. Ocular and bulbar muscles are most commonly involved, but any pattern of weakness may be seen. There may also be fatigability in the symptoms, such that the weakness worsens later in the day.

MYASTHENIC CRISIS

Myasthenic crisis occurs when a patient experiences an acute episode of weakness related to the patient's myasthenia gravis that is severe enough to necessitate intubation. As noted previously, respiratory failure occurs because of the weakness of respiratory muscles. Severe oropharyngeal muscle (bulbar) weakness can be part of a patient's myasthenic crisis, and in some it is the predominant finding. When the respiratory musculature fails or when bulbar weakness leads to airway compromise, intubation and mechanical ventilation are necessary.

Myasthenic crisis may develop as part of the natural history of the MG. Crisis may also be precipitated by other factors, most commonly a concurrent infection. Other precipitants include

TABLE 67.3 ■ **Drugs to Be Avoided or Used with Caution in Myasthenia Gravis**

Antibiotics	**Psychotropic**
Aminoglycosides	Lithium
Lincomycin	Chlorpromazine
Clindamycin	**Rheumatologic Agents**
Polymyxin B	D-Penicillamine
Colistin/colistimethate	Chloroquine
Bacitracin	**Other**
Antimalarials	Sodium lactate
Chloroquine	Magnesium sulfate
Quinine	Neuromuscular blocking agents
Cardiovascular Agents	Ophthalmic beta-blockers
Quinidine	**Problematic at High Doses**
Procainamide	Opioids
Bretylium	Muscle relaxants
Verapamil	Respiratory depressants
Beta-blockers	CNS depressants
Lidocaine	Corticosteroids

CNS, central nervous system.

the tapering of immunosuppressive medications (such as prednisone), surgery, or certain medications that may worsen MG. Multiple medications can potentially increase weakness in MG (Table 67.3). This is of more concern with certain antibiotics (aminoglycosides, erythromycin and azithromycin), cardiac drugs (beta-blockers, procainamide, and quinidine), and magnesium.

DIAGNOSIS OF MYASTHENIA GRAVIS

Laboratory studies are used to confirm the diagnosis of clinically suspected myasthenia gravis (Table 67.4). Up to 90% of patients have detectable antibodies, which can be tested with a serum assay, either to the acetylcholine receptor (AChR) or muscle-specific kinase (MuSK) at the neuromuscular junction. About 10% of myasthenics do not have either antibody and are classified as having "seronegative" myasthenia gravis.

For patients who are seronegative, or if a long delay is anticipated in getting the serologic study results, the laboratory confirmation of MG can often be made with electrophysiologic (EMG) studies. As part of the EMG study, repetitive nerve stimulation (RNS) studies can readily be performed in the ICU setting. Characteristic abnormalities in the RNS studies are seen in 85% of patients with moderate to severe generalized MG. Single-fiber EMG is a more sensitive technique for identifying MG, but generally it cannot be performed in the ICU because of electrical noise.

Up to 10% of patients with MG have an underlying thymoma. It is recommended that newly diagnosed myasthenics have a chest imaging study performed (e.g., computed tomography [CT] or magnetic resonance imaging [MRI]).

Although edrophonium (Tensilon) testing can be used in outpatients with obvious ocular findings such as ophthalmoparesis or ptosis, there is no role for this bedside test in the ICU setting. Edrophonium is a short-acting acetylcholinesterase inhibitor that is administered intravenously. In patients with ocular symptoms, it will cause a rapid improvement of ocular misalignment or ptosis. It has a sensitivity of ~80% to 90% in patients with prominent ocular findings, but it is associated with many false-negative and false-positive results.

THERAPY

When weakness becomes severe and respiratory failure occurs, treatment with rapid therapies is indicated. Rapid therapies for MG include PE and IVIG (see Table 67.2). PE and IVIG start to work within days, but the benefits last only a few weeks. There are limited data comparing these two forms of rapid therapy for myasthenic crises, but to date there is no convincing difference in the beneficial effects of these therapies in this setting. However, some evidence suggests that

TABLE 67.4 ■ **Suggested Laboratory Tests in Suspected Myasthenia Crisis in the ICU**

Diagnostic Studies	Other Helpful Studies
AChR and MuSK antibody titers (90%)*	Chest computed tomography for thymoma
EMG with RNS (80%)*	Thyroid function studies
	Autoimmune screen (if clinical suspicion)
	Workup for acute infection that triggered crisis
	Screen for conditions that may complicate steroid therapy†

*Indicates approximate sensitivity of test in generalized MG.
†Examples include tuberculosis, diabetes, peptic ulcer disease, hypertension, and renal disease.
AChR, acetylcholine receptor; MuSK, muscle-specific kinase; EMG, nerve conduction studies and needle electromyography; RNS, repetitive nerve stimulation.

PE works more quickly than IVIG in seriously ill patients with myasthenia; as a result, many neuromuscular experts prefer PE as a first-line therapy. Others prefer IVIG because it is easier to administer and, other than perhaps the onset of action, has similar efficacy as PE.

In most patients, initiation of high-dose corticosteroids concurrently is also necessary, in that the steroids begin to have effects after 2 to 3 weeks as the PE or IVIG effect wears off. However, high-dose corticosteroids can actually cause a paradoxical worsening of myasthenic symptoms during the first 5 to 10 days of treatment, unless they are used concurrently with PE or IVIG. Thus, high-dose corticosteroids should not be used in the setting without the initiation of PE or IVIG first.

In general, one should withhold anticholinesterase medications in the ICU setting until the patient has been extubated and is clearly improving. This limits the bothersome side effect of excess secretions in a patient with an impaired airway or on mechanical ventilation. An excess of anticholinesterase medications can cause weakness that may look like worsening MG. This paradoxical weakening is an entity called "cholinergic crisis." However, cholinergic crisis is not seen when doses are limited to the usual pharmacologic range, < 120 mg of pyridostigmine every 3 hours. It is such a rare entity that it should not be assumed to be the cause of a patient's weakness unless the doses used are known to significantly exceed this range. At pharmacologic doses, even in the presence of cholinergic side effects, it should be assumed that the patient's underlying MG is worsening and appropriate treatment should be initiated.

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CHAPTER 68

Brain Death and Management of Potential Organ Donors

Joshua M. Levine ■ Patrick K. Kim

Patients who sustain brain injury from various causes may have irreversible damage to their central nervous system (CNS). When the injury is sufficiently severe to damage the cortex and brain stem with disruption of normal responsive and homeostatic mechanisms, the patient may meet the criteria for "brain death" (i.e., death by neurologic criteria). All states in the United States accept brain death as legally valid, and most have statutes modeled after the Uniform Determination of Death Act. The latter states:

> *An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made in accordance with accepted medical standards.*

This chapter discusses those accepted medical standards and how to test for them.

Making a timely and accurate diagnosis of brain death is an essential skill of intensivists. It is important for several reasons: (1) caring for the family's needs, (2) allocating limited intensive care unit (ICU) resources fairly and wisely, and (3) providing opportunities for organ donation. In general, it requires a review of the patient's medical history, two neurologic examinations, and, in some circumstances, the use of a confirmatory diagnostic test (Figure 68.1).

Although there are no national standards for brain death determinations, as a rule, hospitals have incorporated these elements into their policies and protocols concerning brain death. However, heterogeneity still exists in practice across institutions. It is therefore incumbent on ICU physicians to be familiar with their institutional policies.

Determination of Brain Death

MEDICAL HISTORY

The initial evaluation of the potentially brain dead patient should focus on the patient's history (see Figure 68.1). There should be an identifiable and reasonable cause to explain the patient's current condition. Next, the clinician must exclude reversible causes of coma, such as toxic or metabolic causes. Any such confounding condition must be corrected before continuing the evaluation. These include gross physiologic disturbances, such as hypothermia, hypoxemia, and hypotension or circulatory shock; metabolic derangements, such as acidosis, hypo- or hyperglycemia, and renal or hepatic encephalopathy; and serious electrolyte disorders, such as hypo- or hypernatremia and hypo- or hypercalcemia.

Drug overdose or toxic exposure should always be ruled out in patients presenting to the ICU in coma and who otherwise appear brain dead. In most cases, if a patient has received sedatives or analgesics before the evaluation for brain death, adequate time (usually four times the excretion half-life of the substance, taking into account hepatic or renal dysfunction when present) for elimination of the substance must occur.

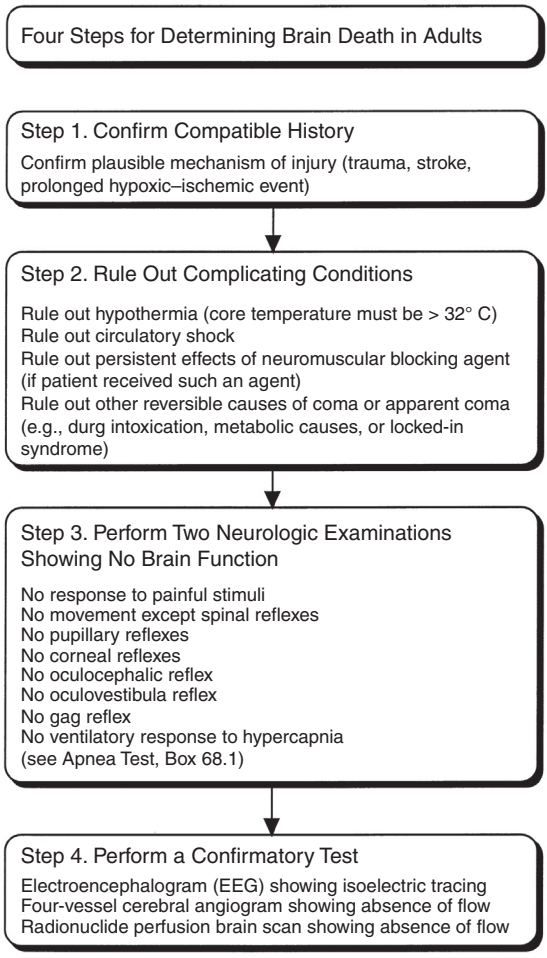


Figure 68.1 Recommended steps in making a brain death determination (see text for details). Intervals between two neurologic examinations should be at least 24 hours in cases of hypoxic-ischemic brain injury and at least 12 hours in other types of brain injury. The second examination can be omitted if the four-vessel cerebral angiogram or perfusion brain scan confirms no flow to the brain. Consistent with policies of many hospitals, a confirmatory test, usually an electroencephalogram (EEG), is recommended for *all* patients undergoing brain death determination.

Particular attention must be given to patients in whom neuromuscular blocking agents were used to ensure they have been adequately cleared from the circulation (see Chapter 5). A peripheral nerve stimulator should be used in all patients undergoing evaluation for brain death who received neuromuscular blocking agents.

PHYSICAL EXAMINATION IN BRAIN DEATH DETERMINATION

Brain death is a clinical diagnosis whose cardinal features are (1) coma, (2) absence of brain stem reflexes, and (3) apnea. Because of the critical role of the examination, many hospitals mandate consultation with a neurologist when patients are not already on a neurologic or neurosurgical service.

Coma

For the purpose of brain death determination, coma is defined as the absence of observable responses to noxious stimuli, other than those produced by spinal cord reflexes. Coma manifests as lack of cerebral

motor activity in response to pain in all four extremities and the head. Stimuli of sufficient intensity should be used such as strong pressure to the nailbeds and the supraorbital ridges. Grimacing, moaning, or nonstereotyped movements are inconsistent with brain death.

ABSENCE OF BRAIN STEM REFLEXES

Pupillary reflexes should be assessed in a dimly lit room with the patient's eyes initially closed. The eyes are opened and a bright light is applied sequentially to each pupil. The pupils should be observed for 30 seconds. A normal response is brisk constriction of the pupil. In brain death, the pupils must be nonreactive ("fixed") and midsized. Excessively large or excessively small pupils should raise suspicion for drug intoxication.

The *corneal reflex* can be assessed by lightly touching the cornea with a sterile cotton swab or gauze. A normal response is a blink to the stimulus. In brain death, there should be no response.

The *oculocephalic reflex* ("doll's eye reflex") assesses vestibular and proprioreceptor responses. In an intact reflex, as the patient's head is rotated laterally from one side to the other, the patient's eyes move in the opposite direction. In a brain dead patient, the eyes remain fixed with the lateral turn. This maneuver should not, however, be performed in patients with potentially unstable cervical fractures.

The *oculovestibular reflex* (cold caloric reflex) assesses vestibular and midbrain functions but generally provides a stronger stimulus than the oculocephalic reflex. The external auditory canals should first be inspected to ensure that the tympanic membranes are intact and unobstructed. The head should be midline and elevated at 30 degrees to allow for maximal stimulation of the horizontal semicircular canal. A soft catheter is inserted into the canal and the ear is slowly (20 seconds or more) irrigated with at least 50 mL of iced water. The eyes are observed for ~1 minute. If the reflex is intact, both eyes deviate toward the irrigated ear followed by nystagmus with the fast phase beating away from the irrigated ear. In a brain dead patient, the eyes do not move at all. Any other response is not consistent with brain death.

The *cough and gag reflexes* test the integrity of the medulla and the lower cranial nerves (IX, X). The cough reflex is elicited by stimulating the carina with a deep suction catheter that is passed through the endotracheal tube. Normally this produces a vigorous cough. In a brain dead patient there should be no response. The gag reflex may be tested by gently tugging on the endotracheal tube. In many normal people this will produce gagging; in the brain dead patient, there is no response.

The *apnea test* is used to confirm brain death clinically only when the aforementioned preconditions have been met and when all other brain stem reflexes are absent. Because it requires an intact phrenic nerve and functioning diaphragm, it should not be performed if patients have a high cervical fracture or neuromuscular disease impairing diaphragmatic function. Maintaining adequate oxygenation during the test and documenting a rise in $Paco_2$ to a level that would stimulate respiration in an intact patient is critical to performing a successful apnea test (Box 68.1).

CONFIRMATORY TESTING IN BRAIN DEATH

Certain techniques that assess brain electrical activity or cerebral blood flow have been established as confirmatory tests for brain death. In general for adults, brain death is a clinical diagnosis and confirmatory tests are unnecessary. However, institutional polices differ and in some hospitals these tests may be mandatory. Confirmatory tests are most useful when conditions exist that interfere with the clinical assessment, such as severe facial trauma, preexisting pupillary abnormalities, and toxic levels of certain medications. Some protocols allow for an expedited diagnosis of brain death (i.e., a shortened interval between clinical examinations) when confirmatory tests are obtained. This may be useful in potential organ donors.

BOX 68.1 ■ Steps in Performing the Apnea Test

1. Preoxygenate patient with 100% oxygen for at least 15 minutes.
2. Confirm that arterial pH ≤ 7.44 and $Paco_2$ = 35 to 45 mm Hg at the start of the test.
3. Disconnect patient from the ventilator and give supplemental oxygen to keep Sao_2 at 98%. (This can be done by T piece or, preferably, by delivering oxygen at 2 to 6 L/min via a 14 Fr suction catheter [with its proximal suction port taped closed] inserted into the endotracheal tube until it is 1 to 2 cm above the tip of the endotracheal tube.)
4. Observe patient for spontaneous respiratory efforts for 10 minutes.
5. After 10 minutes, obtain an arterial blood gas sample and place patient back on mechanical ventilation ($Paco_2$ can be expected to rise 2 to 4 mm Hg/min in the absence of ventilation).
6. $Paco_2$ at the end of the observation period should be at least 60 mm Hg. If not, repeat the test with a longer observation period.
7. For patients who lack a normal response to elevated $Paco_2$ (chronic obstructive pulmonary disease with baseline hypercapnia or obesity hypoventilation syndrome), follow the hospital policy dealing with such circumstances or perform a confirmatory test without attempting the apnea test.

Note: The apnea test should be performed only after the absence of other brain stem reflexes has been documented on both the first and second neurologic examinations because it may aggravate hemodynamic instability.

Electroencephalography (EEG) in brain death is characterized by an isoelectric recording referred to as electrocerebral inactivity or silence. An isoelectric recording can also occur in patients who have received toxic levels of CNS depressants. This emphasizes the importance of eliminating the possibility of potentially confounding conditions (see Figure 68.1) before establishing the diagnosis of brain death. The recording must be made in accordance with the appropriate specifications and be performed under the supervision of a neurologist familiar with these protocols.

Cerebral evoked responses, including brain stem auditory evoked responses recorded after auditory click and somatosensory evoked responses recorded after median nerve stimulation, assess whether specific brain stem pathways are intact. These tests may be used to predict poor outcome in comatose patients after hypoxic-ischemic injuries (see Chapter 70), but their usefulness as a confirmatory test for brain death remains to be established.

Not surprisingly, the absence of cerebral blood flow strongly correlates with clinical brain death and pathologic evidence of brain necrosis. Brain blood flow can be assessed by a number of imaging methods including conventional cerebral angiography, nuclear blood flow scans, and transcranial Doppler ultrasonography (TCD).

Failure to visualize the intracranial vessels after intravenous injection of radiocontrast is considered to be the gold standard confirmatory test for the diagnosis of brain death. Unfortunately, the cost of the study, the risk of transporting the patient to the radiology department, and the potential nephrotoxicity of the contrast limit its routine use. Radionuclide imaging with technetium (Tc^{99m}) or iodine (I-123)-based agents is safe, accurate, and can be performed at the bedside of the critically ill patient. Because its resolution is less than conventional angiography, it really can only assess for the presence or absence of cerebral cortical flow and not brain stem flow. Under most conditions, however, when used in conjunction with the findings of the clinical examination (see Figure 68.1), absence of nuclide uptake within the brain is accepted as diagnostic for brain death. TCD may detect various patterns that are consistent with brain death including short systolic spikes and reversal of flow during diastole. Computed tomography (CT) angiography has been studied as a confirmatory test. As in conventional angiography, the absence of intracranial blood flow would theoretically support the diagnosis of brain death. Although a promising modality, further studies are needed before CT angiography becomes widely accepted as a confirmatory test.

Finally, because death is a legal as well as medical event, as noted earlier, one must know how the laws of one's particular jurisdiction influence making brain death determinations. Although uncommon, one may encounter local statutes that conflict with what is presented in this chapter because not all states or countries treat brain death uniformly.

Communication with the Family

Although procedures to determine brain death have become well established in most ICUs in the United States, two major problems persist. One has to do with coping successfully with the challenges of medical management of the brain dead patient, which is addressed later in this chapter. The other has to do with dealing with the family's lack of understanding about brain death as communicated to them by the ICU team.

How the concept of brain death and its implications for organ transplantation are communicated to the patient's family leaves a great deal of room for improvement. For example, one survey of families of brain dead patients found that 52% of nondonor families (those who refused organ donation) still believed that *a brain dead patient could recover*. Indeed, 39% of donor families and 47% of nondonor families said that they *never* received an explanation about brain death from a physician or other health care professional. It should not be difficult to understand why a family that does not comprehend that brain death equates to human death would refuse to donate that patient's organs.

Management of the Potential Organ Donor

GOALS OF AGGRESSIVE MANAGEMENT

The goal of aggressive management is to maintain organs suitable for transplantation in the brain dead patient while waiting for permission for transplantation and until transfer of the patient's care to the transplantation team in the operating suite.

Despite increased interest in using ICU patients as non–heart-beating cadaveric donors after their life support is withdrawn, the greatest supply of organs for donation comes from brain dead donors with an intact circulation. Experience has shown that aggressive management of the potential organ donor during and after determination of brain death can increase the total number of successful donors and the number of organs procured per donor. The importance of this effort cannot be overemphasized because the gap between the number of patients awaiting transplants and the number of available organs continues to widen.

Without aggressive support, studies have shown that cardiac arrest occurs in 20% of potential organ donors within 6 hours of making the determination of brain death and in 50% of potential organ donors within 24 hours of brain death. Although a complete description of organ procurement procedures is beyond the scope of this chapter, knowledge of the anticipated physiologic disorders in the brain dead patient and an organized approach to the patient's treatment are essential to all intensivists (Table 68.1).

In many ICUs, clinically savvy members of the regional organ procurement organization (OPO) can assist the ICU team in the medical management of the brain dead patient, such as by providing written protocols to guide this therapy.

Loss of Homeostatic Mechanisms

As described previously, loss of homeostatic mechanisms is the hallmark of brain death. For this reason, hypothermia is common in these patients and must be treated aggressively with active rewarming. Rewarming techniques include the use of external warming devices, warmed saline gastric lavage, and warming ventilator gases to 40° to 41° C (see also Chapter 56).

TABLE 68.1 ■ **Physiologic Complications of Brain Death**

Disordered System	Manifestations
Central homeostasis	Hypothermia
Cardiopulmonary	Autonomic "storm" with hypertension and tachycardia
	Subsequent hypotension with loss of vascular tone
	Bradycardia or tachycardia
	Pulmonary edema
Endocrine	Central diabetes insipidus
	Hypothyroidism
	Adrenal insufficiency
Hematologic	Disseminated intravascular coagulopathy

Cardiovascular Changes

Cardiovascular changes in brain death include an initial sympathetic "storm" with associated hypertension and tachycardia followed by profound hypotension requiring intensive interventions. Before cessation of brain stem function, as intracerebral pressure rises, the medulla oblongata becomes ischemic. This results in unopposed sympathetic activity, which causes significant hypertension and tachycardia. This is frequently brief and often does not require intervention with antihypertensive agents.

Soon after brain death, hypotension frequently occurs from several factors. Absolute hypovolemia can be present because of traumatic fluid loss, third spacing, diabetes insipidus (DI), or the use of diuretics for the treatment of cerebral edema. Neurogenic shock characterized by a loss of vascular tone and venous pooling can also occur from a loss of central vasomotor control. Initial therapy should be volume replacement with isotonic crystalloid. Blood products may be used if the hemoglobin is less than 10 g/dL or if there is a coexisting coagulopathy warranting therapy. In patients who do not respond to volume loading, vasoactive agents should be added. In patients who have pulmonary edema, cardiac dysfunction, persistent hypotension, or high positive end-expiratory pressure (PEEP) requirements, insertion of a pulmonary artery catheter to guide therapy should be considered.

Endocrine and Fluid-Electrolyte Changes

Central DI occurs commonly after brain death because of a lack of central secretion by the pituitary gland. It is defined by hypernatremia, hyperosmolar plasma, and hypotonic polyuria (> 4 mL/kg/h). If untreated, DI can result in hypovolemia and such severe electrolyte abnormalities that the patient's organs are deemed unacceptable for transplantation.

Therapy for DI involves replacement of water losses and arginine vasopressin. The water replacement should be based on the calculated free-water deficit (see Chapter 85), but a good starting point is to infuse replacement sodium-free fluid at the rate of the urinary output from the previous hour. If dextrose-containing solutions are used, care must be taken to avoid hyperglycemia. Arginine vasopressin (AVP) should be given with urine outputs > 200 mL/h. Administered as an aqueous intravenous (IV) infusion, AVP should be titrated to decrease urine output to 100 to 200 mL/h. This is usually in the range of 0.5 to 1.0 units/h. Patients who require prolonged therapy are candidates for desmopressin (DDAVP), a synthetic vasopressin analogue with less pressor effect.

Electrolyte abnormalities should be monitored and treated when present. Although circulating thyroid hormone (thyroxine) and cortisol levels have been shown to decrease after brain death, replacement therapy is generally not routinely recommended, although management protocols by

some organ procurement organizations may include such interventions. Glucocorticoid replacement should, however, be considered in cases of refractory hypotension.

Involving the Regional Organ Procurement Organization

According to many state laws, obtaining consent for transplantation from family members, screening potential organ donors, and deciding on organ allocation are the responsibilities of representatives of regional organ procurement organizations. In addition, the appropriate organ procurement organization should be made aware of all potential organ donors undergoing brain death determinations to maximize timely and coordinated interactions among all relevant parties.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 69

Neurologic Assessment and Prognosis after Cardiopulmonary Arrest

Ting Zhou ■ Joshua M. Levine

Advances in cardiopulmonary resuscitation (CPR), emergency medical systems, and intensive care have been associated with increased rates of return of spontaneous circulation (ROSC) after cardiac arrest. The neurologic prognosis for survivors, however, remains poor. Approximately 80% of survivors are initially comatose. Of those who survive beyond hospital discharge, good neurologic recovery occurs in only 10% to 30%, and less than 10% resume their former lifestyle. The primary determinant of outcome in survivors of cardiac arrest is the degree of functional neurologic recovery. A wide spectrum of possible neurologic outcomes exists, ranging from brain death to complete recovery. Familiarity with the natural history of cardiac arrest and prognostic indicators of neurologic recovery is essential for clinicians in intensive care units (ICUs) in order to advise families about goals of further care that respect the patient's preferences and values.

This chapter describes the natural history, clinical neurologic assessment, and prognosis of comatose survivors of cardiac arrest. Predictors of outcome are disease specific; prognostic indicators used for patients with cardiac arrest cannot reliably be applied to patients with coma from other causes, such as trauma, stroke, and toxic or metabolic derangements.

States of Consciousness after Cardiac Arrest

The central nervous system (CNS) is exquisitely vulnerable to ischemia and circulatory arrest. Brain injury from global ischemia or circulatory arrest is termed *hypoxic–ischemic encephalopathy.* Cognitive, motor, and sensory abnormalities develop and recover after cardiac arrest with tremendous variability in rate and degree. In general, when recovery occurs, brain stem functions return in a caudal-to-rostral progression. First to return are spontaneous respirations and other cranial nerve reflexes. This is followed by the appearance of extensor (decerebrate) posturing, then flexor (decorticate) posturing, and intermittent electrical cortical activity. Defensive motor or verbal responses and increasing levels of consciousness are last to appear. Level of consciousness is frequently used to gauge recovery in the ICU.

States of consciousness fall along a spectrum, with coma at one end and normal consciousness at the other. Patients who are in *coma* exhibit no responses to external stimuli other than reflexive behavior. Their eyes are closed and sleep-wake cycles are absent. Coma is usually prolonged—lasting for at least hours to days, but rarely permanent—eventually progressing either to death or to a higher level of consciousness. In the United States, *brain death* (death by neurologic criteria) refers to the irreversible cessation of whole-brain activity and is legally equivalent to cardiac death. Brain death is a clinical diagnosis whose cardinal features are coma, apnea, and absence of all other brain stem reflexes

Additional online-only material indicated by icon.

(Chapter 68). Those who recover from coma progress through a *vegetative state,* which is distinguished from coma by the presence of episodic eye opening and sleep-wake cycles. Patients in a vegetative state may turn their heads to auditory or tactile stimuli and may produce unintelligible sounds; however, they do not follow commands or exhibit purposeful movements, such as pulling a limb away from painful stimuli. When the vegetative state lasts for more than one month it is termed a *persistent vegetative state,* and when it lasts for more than one year it is termed a *permanent vegetative state*. Those who recover further enter a *minimally conscious state,* characterized by limited awareness of and responsiveness to their environment. In this state, patients inconsistently may track visual stimuli with their eyes, obey simple commands, reach for objects, and at times exhibit purposeful behavior such as crying or smiling. Although somewhat artificial, categorizing level of consciousness may be helpful in assessing the severity of brain injury and in charting the course of neurologic recovery.

Neurologic Examination

The neurologic examination after cardiac arrest aids in the assessment of location and severity of injury, rate of recovery, and prognosis. It is also used to assess for conditions that may confound prognosis, such as toxic or metabolic derangements. Examinations should be performed (and documented) serially over time, as recovery is dynamic. Typically, assessment is focused to evaluate the following four CNS functions: (1) level of consciousness, (2) brain stem function, (3) motor function and abnormal reflexes, and (4) breathing pattern.

Determination of Neurologic Prognosis after Cardiac Arrest

Predicting neurologic outcome after cardiac arrest is challenging. The only reliable predictor of good recovery is rapid awakening after resuscitation (i.e., within minutes to hours). Studies have focused primarily on predictors of poor outcome. Importantly, few studies have included patients treated with *therapeutic hypothermia*, which is now recognized as the standard of care. This section addresses traditional methods of prognostication and also covers what is currently understood about prognostication in cardiac arrest patients who have been treated with hypothermia.

Many studies have assessed predictors of outcome in the comatose patient after CPR. Most have been retrospective analyses of a cohort of patients. The outcomes measured have usually been overall patient survival and neurologic recovery. The degrees of recovery and level of neurologic function were defined similarly (Table 69.1). Predictors of outcome that have been studied include

TABLE 69.1 ■ **Levels of Neurologic Recovery**

Level	Description
No recovery	Coma until death
Vegetative state	Eyes-open wakefulness without evidence of cognitive awareness
Severe disability	Conscious but dependent on others for performing ADLs
Moderate disability	Conscious but unable to resume the prior level of activity (but not dependent on others for ADLs)
Good recovery	Resumes prior level of activity and function

ADLs, activities of daily living (to move from bed to chair, to walk, to change one's clothes, and to feed, bathe, and toilet oneself).

Data from Levy DE, Caronna JJ, Singer BH, et al: Predicting outcome from hypoxic-ischemic coma. JAMA 253:1420-1426, 1985.

LEVEL OF CONSCIOUSNESS

Assessment of level of consciousness begins with observation. Patients who exhibit spontaneous eye opening, verbalization attempts, moaning, tossing, reaching, leg crossing, yawning, coughing, or swallowing have a higher level of consciousness than those who do not. The examiner should next assess the patient's response to a series of stimuli that escalate in intensity. The patient's name should be called loudly. If there is no response, the examiner should stimulate the patient by gently shaking him. If this produces no response, the examiner must use a noxious stimulus, such as pressure to the supraorbital ridge, nail beds, or sternum, or nasal tickle with a cotton wisp. Responses such as grimacing, eye opening, grunting, or verbalization should be documented. Motor responses provide information not only about sensation and limb strength but also about level of consciousness. The examiner should note whether stimuli produce "purposeful," or non-stereotyped limb movements—such as reaching toward the site of stimulation ("localization"). This implies a degree of intact cortical function. Stereotyped limb movements are generally mediated by brain and spinal reflexes and do not require cortical input. Examples include extension and internal rotation of the limbs (decerebrate posturing), upper extremity flexion (decorticate posturing), and flexion at the ankle, knee, and hip ("triple-flexion").

BRAIN STEM FUNCTION

Brain stem integrity is assessed by examination of the cranial nerves. The pupillary light reflex involves cranial nerves II and III and evaluates midbrain function. Pupillary size, shape, and reactivity to light should be noted. The pupils are normally round, have equal diameters, and briskly constrict when illuminated. In general, abnormalities of the pupillary light reflex suggest a structural abnormality. However, drugs that are frequently administered during resuscitation and in the ICU may also affect the pupillary light reflex. Bilaterally fixed and dilated pupils are seen with brain death but also with anticholinergic medications, such as atropine. Hyperadrenergic states (e.g., pain, anxiety, cocaine intoxication) produce bilaterally large and reactive pupils. Reactive pinpoint (< 1 mm) pupils are observed with opioid usage or intoxication. Pupil size, shape, and reactivity might provide clues to the presence of intoxicants that might otherwise confound neurologic assessment.

Cranial nerve II (optic nerve) should also be evaluated by direct visualization. A funduscopic examination should be performed to look for signs of intracranial hypertension. Papilledema is swelling of the optic nerve head from increased intracranial pressure. It is almost always bilateral and may be accompanied by retinal hemorrhages, exudates, cotton wool spots, and ultimately by enlargement of the optic cup. Papilledema develops over hours to days. Its absence, therefore, does not imply normal intracranial pressure, especially in the acute setting. Pulsatility of the retinal veins strongly suggests normal intracranial pressure, whereas the absence of pulsatility is noninformative.

Eye position and spontaneous movements should be noted. Horizontal or vertical misalignment of the eyes should be documented as well as spontaneous roving or rhythmic and repetitive vertical movements. Regions of cortex in the frontal and parietal lobes ("eye fields") mediate conjugate deviation of the eyes toward the contralateral side. Lateral deviation of both eyes therefore indicates a destructive lesion in the ipsilateral cortex or, as may be more common after cardiac arrest, an excitatory focus (seizure) in the contralateral hemisphere. Dysconjugate gaze is frequently seen in sedated patients and usually represents unmasking of a latent esophoria or exophoria. Roving or slow to-and-fro eye movements imply functional integrity of the brain stem. There is a high incidence of nonconvulsive seizures in comatose patients after cardiac arrest, and jerking movements of the eyes or a forced conjugate deviation may be the only clinical evidence of seizure activity.

If spontaneous eye movements are absent, then an oculocephalic response ("doll's eyes") should be sought by turning the head rapidly both horizontally and vertically. The oculocephalic reflex interrogates function of the vestibular nuclei (pons) and its connections to the ocular motor nuclei (midbrain and pons). This maneuver should not be performed on patients with known or suspected cervical spine instability. Normally the eyes move opposite the direction of head turning. If an oculocephalic response cannot be elicited, then an oculovestibular ("cold-caloric") response is sought. First, the tympanic membrane should be visualized to ensure that it is intact and unobstructed. The head of the bed should be set at a 30-degree angle to align the patient's horizontal semicircular canals parallel to the floor. Then, using an angiocatheter or a butterfly catheter without the needle, 30 to 60 mL of ice-cold water are instilled into the external auditory canal against the tympanic membrane. This inhibits the ipsilateral vestibular system and normally causes the eyes first to move slowly toward the ipsilateral ear and then to jerk quickly toward the contralateral ear. The initial slow response is mediated by the unopposed contralateral vestibular system in the brain stem, and the subsequent corrective nystagmus is mediated by the cortical eye fields. With bilateral cortical dysfunction and an intact brain stem, slow tonic deviation of the eyes toward the ipsilateral ear is observed and is not followed by contralateral nystagmus. Complete absence of any response indicates diffuse brain stem dysfunction and may be seen in cardiac arrest patients during late stages of transtentorial herniation, barbiturate intoxication, or brain death.

The corneal reflex evaluates cranial nerves V and VII (pons) and is tested by gently touching the cornea of each eye with a drop of saline or a cotton wisp and observing for bilateral eyelid closure. The cough and gag reflexes and spontaneous respirations are mediated by the medulla. The cough reflex may be evaluated by stimulation of the carina with a suction catheter. The gag reflex is tested by stimulation of the posterior pharynx (with a tongue depressor or cotton swab) or by gently tugging on the endotracheal tube. To determine whether spontaneous respirations are present, the patient should be observed for overbreathing the ventilator (i.e., breathing at a respiratory rate higher than the rate set for the ventilator) and pressure tracings should be examined for spontaneous (patient) effort. Breathing patterns are discussed later.

MOTOR FUNCTION AND ABNORMAL REFLEXES

The symmetry of motor responses and reflexes or the presence of abnormal movements often allows discrimination between structural and systemic etiologies of altered mental status in the cardiac arrest patient. First, the patient should be observed for any abnormal or spontaneous movements. Asterixis implies a metabolic disturbance such as uremia or hepatic encephalopathy. Twitching or jerking of the face or limbs, even if subtle, raises the suspicion for seizures. Decorticate posturing may imply injury above the red nucleus (midbrain), whereas decerebrate posturing may imply injury below.

BREATHING PATTERNS

A variety of breathing patterns may be observed in patients with hypoxic-ischemic encephalopathy. Although these may yield clues regarding the location of the intracranial lesion, in clinical practice, breathing patterns are often obscured by the use of sedatives, paralytics, and mechanical ventilation. Apneustic respirations are characterized by a prolonged end-inspiratory pause. This pattern may be seen after focal injury to the dorsal lower half of the pons (e.g., stroke) but may also be observed with meningitis, hypoxia, and hypoglycemia. Cluster breathing consists of several rapid, shallow breaths followed by a prolonged pause, and it localizes to the upper medulla. Ataxic respirations, or Biot's breathing, is a chaotic pattern in which the length and depth of the inspiratory and expiratory phases are irregularly irregular. It may occur after injury to the respiratory centers in the lower medulla and is a preterminal pattern. Apnea may be seen in a variety of neurologic and non-neurologic disorders

and is of no localizing value. Kussmaul respirations are rapid, deep breaths that usually signal metabolic acidosis but also may be observed with pontomesencephalic lesions. Cheyne-Stokes respirations refer to alternating spells of apnea and crescendo-decrescendo hyperpnea. It has minimal value in localization and is seen with diffuse cerebral injury, hypoxia, hypocapnia, or congestive heart failure. Agonal gasps reflect bilateral lower medullary injury and are seen in the terminal stages of brain injury.

neurologic signs followed sequentially postarrest, circumstances of arrest, electrophysiologic studies, brain imaging, and biochemical markers.

THE LEVY CRITERIA

Until therapeutic hypothermia was in use, the Levy criteria (published by Levy et al in 1985) were used to predict neurologic outcome. In this landmark prospective cohort study of more than 200 comatose patients after nontraumatic coma (71% of these cases were directly attributable to cardiac arrest), Levy and colleagues devised a set of prognostic algorithms based on neurologic examination findings at various time points (initial assessment [within 6 to 12 hours], 1 day, 3 days, 7 days, and 14 days). The stratification of patients according to their physical findings and predicted 1-year best neurologic recovery is summarized in Tables 69.E1 and 69.E2.

The Levy criteria have fallen out of favor as a tool for determining prognosis, primarily because of study flaws as well as clinical and scientific advances since their publication in 1985. Study flaws include (1) limited generalizability because of the small sample size, and inclusion of data from only one institution, (2) internally inconsistent definitions and categorizations of levels of consciousness, (3) possible inclusion of patients in whom care was intentionally limited, and (4) lack of corroboration in other large cohort studies. Furthermore, concern has been raised about using examination findings for prognosis that are likely confounded by the use of sedative medications, neuromuscular blocking agents, and metabolic derangements, all of which are frequently encountered. Since publication of the study, subsequent prospective studies and clinical advances in resuscitation, emergency room, and ICU management raise further concern that the Levy criteria have limited utility at best and have become obsolete.

In the modern era, two authoritative evidence-based practice parameters guide the determination of prognosis after cardiac arrest. The American Academy of Neurology (AAN) published recommendations in 2006, and the American Heart Association (AHA) published recommendations in 2010. Both sets of guidelines examined the evidence for a variety of potential prognostic indicators to determine that they had a sufficiently low false-positive rate (near zero) to be used as reliable indicators of poor prognosis. Between the two publications, indicators evaluated included CPR-related variables, elevated body temperature, the presence of myoclonic status epilepticus, features of the neurologic examination, electroencephalography (EEG) findings, somatosensory evoked potential (SSEP) findings, serum biomarkers, cerebral physiologic parameters (intracranial pressure, brain tissue oxygen tension), and neuroimaging findings. Both guidelines advise against making prognostic judgments during the first 24 hours after cardiac arrest and mandate that confounding variables (e.g., sedatives, paralytics, hypotension) be excluded. Both guidelines suggest that the neurologic examination and SSEP provide useful prognostic information, but that neuroimaging results (computed tomography [CT] or magnetic resonance imaging [MRI]) should *not* be relied on for prognosis.

Although the two guidelines are in general agreement, there are important differences. The AAN guidelines state that prognosis is poor if any of the following are present: myoclonus status epilepticus after day 1, absent N20 (cortical) waves bilaterally on SSEP on days 1 to 3, serum neuron-specific enolase (a biomarker) level > 33 μg/L on days 1 to 3, or absent pupillary light reflexes *or* corneal reflexes or extensor or absent motor responses on day 3. Figure 69.1 and Table 69.2 summarize the AAN prognostication algorithm.

The AHA guidelines state that absence of both corneal *and* pupillary light reflexes ≥ 72 hours after cardiac arrest can be used to infer poor prognosis, as can bilateral absence of N20 waves on SSEP. After 24 hours, certain EEG patterns, such as generalized suppression, burst suppression associated with generalized epileptic activity, or diffuse periodic complexes on a flat background, also suggest poor prognosis. Good outcome is generally seen with early recovery of cortical activity and EEG background reactivity. The AHA guideline recommends *against* using biomarkers, specifically neuron specific enolase (NSE), as a prognostic tool. This is due to variability in assays and reference

TABLE 69.E1 ■ **Best Predictors of Poor Outcomes after Hypoxic-Ischemic Injury**

Time Since Onset of Coma	Physical Findings Present	Percentage in Coma or Vegetative State at 1 Year (95% CI)*	Percentage with Severe Disability at 1 Year (95% CI)	Percentage with Moderate Disability or Good Recovery (95% CI)
Initial examination (6–12 hr)	Absent pupillary light reflex	94 (84–99)	6 (1–16)	0 (0–7)
1day	Motor responses no better than flexor *and* spontaneous eye movements were neither orienting nor roving conjugate	95 (88–98)	4 (84–98)	1 (0–6)
3 days	Motor response no better than flexor	93 (84–98)	7 (2–16)	0 (0–5)
1 wk	Motor response not obeying commands *and* initial spontaneous eye movements were neither orienting nor roving conjugate *and* eye opening at 3 days was not spontaneous†	100 (87–100)	0 (0–13)	0 (0–13)
2 wk	Oculocephalic response not normal *and* motor response was not obeying commands at 3 days *and* eye opening has not improved at least two grades†	100 (80–100)	0 (0–20)	

*95% confidence limits. See Table 69.2 for definitions of outcomes.
†Note that prognosis at the indicated interval is based, in part, on findings at an earlier time point.
Data from Levy DE, Caronna JJ, Singer BH, et al: Predicting outcome from hypoxic-ischemic coma. JAMA 253:1420-1426, 1985.

TABLE 69.E2 ■ **Best Predictors of Good Outcomes after Hypoxic-Ischemic Injury**

Time Since Onset of Coma	Physical Findings Present	Percentage in Coma or Vegetative State at 1 Year (95% CI)*	Percentage with Severe Disability at 1 Year (95% CI)	Percentage with Moderate Disability or Good Recovery (95% CI)
Initial examination (6–12 h)	Pupillary light reflex present *and* motor response extensor or better *and* spontaneous eye movements roving conjugate or orienting	41 (22–61)	19 (6–38)	41 (22–61)
1 day	Motor response withdrawal or better *and* eye opening improved at least 2 grades†	7 (1–22)	3 (0–17)	63 (44–80)
3 days	Motor response withdrawal or better *and* spontaneous eye movements normal	8 (1–25)	15 (4–35)	77 (56–91)
1 wk	Motor response obeying commands	6 (1–21)	22 (9–40)	72 (53–86)
2 wk	Oculocephalic response normal	4 (0–20)	15 (4–35)	81 (61–93)

*95% confidence limits. See Table 69.2 for definitions of outcomes.
†Note that prognosis at the indicated interval is based, in part, on findings at an earlier time point.
Data from Levy DE, Caronna JJ, Singer BH, et al: Predicting outcome from hypoxic-ischemic coma. JAMA 253:1420-1426, 1985.

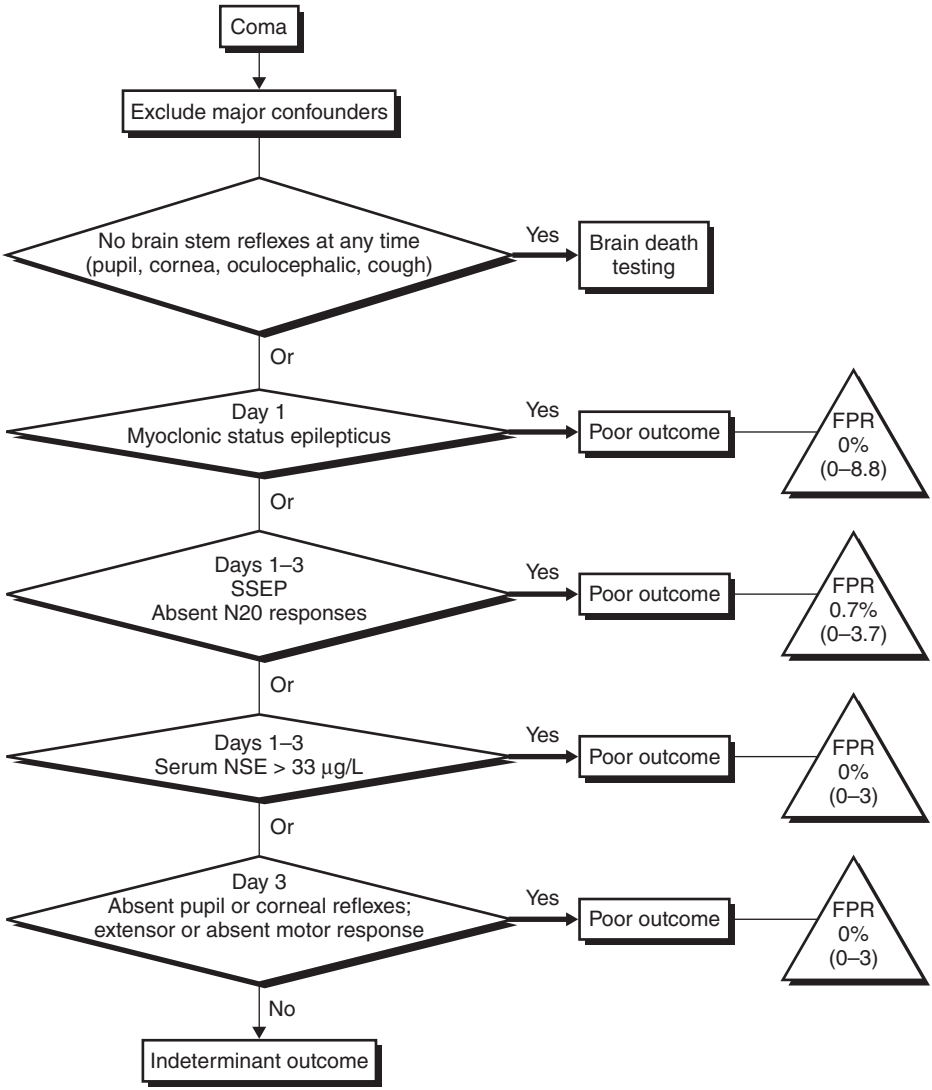


Figure 69.1 AAN Practice Parameters: Decision Algorithm for prognostication of comatose patients after cardiopulmonary arrest. Major confounders include the use of neuromuscular blocking agents, sedatives, induced hyperthermia, presence of organ failure or shock. FPR denotes false positive rate. The numbers in parentheses are 95% confidence intervals. *(Data from Wijdicks EFM, Hijdra A, Young GB, et al: Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation [an evidence-based review]. Neurology 67:203, 2006.)*

values among different centers such that a cutoff value that had no false positive results using one laboratory's assay may be misleading if applied to results from other methods of doing the assay.

PROGNOSTICATION AFTER THERAPEUTIC HYPOTHERMIA

In 2002, the Hypothermia after Cardiac Arrest Study Group and Bernard et al published randomized controlled studies both of which found that therapeutic-induced mild hypothermia

TABLE 69.2 ■ **AAN Practice Parameters: Predictors of Outcome**

Outcome Predictor	Findings	Recommendation
Circumstances of arrest (anoxia time, duration of CPR, cause of the cardiac arrest, cardiac arrhythmia)	Related to poor outcome, but cannot be used to discriminate accurately between patients with poor and those with favorable outcomes because of unacceptably high FPR	Prognosis cannot be based on circumstances of CPR (level B)
Hyperthermia (tympanic thermometry measured above 37.0° C)	Positive association between elevated temperature and poor outcome, but cannot be used alone to identify patients with poor outcome	Prognosis cannot be based on elevated body temperature alone (level C)
Glasgow Coma Scale score	Motor component of the CVS score is more useful and accurate than the GCS sum score; GCS sum score < 2 may give false predictions. GCS motor score < 2 after 72 hrs gives no false predictions	Absent or extensor motor responses after 3 days accurately predict poor outcome (level B)
Brain stem reflexes (pupillary, corneal, and oculocephalic reflex)	No false predictions from absent pupillary response at days 1 to 3, or absent corneal reflex at day 3, or absent eye movements at day 3	Accurate physical examination predictors of poor outcome: Absent pupillary response at days 1 to 3, absent corneal reflexes at day 3, absent eye movements at day 3 (level B)
Myoclonic status epilepticus	Associated with in-hospital death or poor outcome, even in patients with intact brain stem reflexes or some motor responses	Myoclonus status epilepticus within the first 24 hours in patients have a poor prognosis (level B)
EEG	Available data are confounded by different classification systems and variable lengths of recording at different times after arrest; generalized suppression to ≤ 20 μV, burst-suppression pattern with generalized epileptiform activity, or generalized period complexes on a flat background are associated with outcomes no better than persistent vegetative state	Burst suppression or generalized epileptiform discharges on EEG are associated with poor outcome but with insufficient prognostic accuracy (level C)
SSEP	Bilateral absence of N20 components of the SSEP with median nerve stimulation had good predictive value for poor outcome, but optimal timing of SSEP timing remains uncertain	Poor prognosis can be reliably predicted by bilateral absent N20 components of the SSEP with median nerve stimulation within 1 to 3 days after arrest (level B)

TABLE 69.2 ■ **AAN Practice Parameters: Predictors of Outcome** (Continued)

Outcome Predictor	Findings	Recommendation
Serum NSE	In one class I study, all patients with NSE > 33 μg/L after 3 days had poor outcome. However in meta-analysis of all NSE studies, the cutoff point of NSE for an FPR of 0 is greatly imprecise and varied between 20 to 65 μg/L	Serum NSE ≥ 33 μg/L at 1 to 3 days was a predictor of poor outcome (level B)
Other biochemical markers: S100, creatine kinase brain isoenzyme (CKBB)	FPR was 2% and as high as 15% for S100 and CKBB, respectively, as a prognostic indicator	Not enough data to support or refute the prognostic value of other biochemical markers as reliable outcome predictors (level U)
Intracranial pressure (ICP) monitoring and brain oxygenation	Based on small scale studies, ICP > 20 mm Hg in comatose patients is associated with poor outcome, and oxygen glucose index and brain oxygenation may be of value in prognostication	There are inadequate data to support or refute the prognostic value of ICP monitoring (level U)
Brain imaging (CT, MRI of brain)	There are inconclusive data on the predictive information of cerebral swelling on CT scanning; MRI of the brain with DWI and FLAIR sequences showing diffuse cortical signal changes suggests poor prognosis but data are inadequate	Inadequate data to support or refute whether neuroimaging can be used to prognosticate outcome (level U)

Data from Wijdicks EFM, Hijdra A, Young GB, et al: Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review). Neurology 67:203, 2006.

(TIMH) improves survival and functional neurologic outcomes after out-of-hospital cardiac arrest. Since then, hypothermia is regarded as the standard of care for comatose survivors of cardiac arrest. Unfortunately, it is unclear how the performance of prognostic predictors changes in patients treated with TIMH. Studies of prognostic indicators on which the AAN and AHA guidelines were based did not include patients treated with hypothermia. Emerging evidence, primarily from small case series, suggests that many standard predictors lose validity in patients treated with TIMH. It is likely that hypothermia affects neurologic recovery both directly and indirectly, through delayed clearance of commonly used ICU medications that alter neurologic function (e.g., sedatives, neuromuscular blocking agents). No large-scale studies have been conducted that systematically reassess standard predictors of outcome after treatment with TIMH. Both AAN and AHA guidelines warn against the routine application of their results to patients treated with hypothermia.

Small studies have examined the utility of neurologic examination findings as prognostic indicators in cardiac arrest patients treated with hypothermia. These suggest that hypothermia is associated with a delay in motor recovery for up to 6 days. Therefore, absent reflexes or extensor posturing beyond day 3 should *not* be used as an indicator of poor prognosis. Moreover, recovery of brain stem reflexes may be delayed beyond 72 hours and is confounded by the use of sedatives and paralytic medications used to facilitate cooling.

TABLE 69.3 ■ **Recommendations for Care and Prognostication for Neurologic Recovery in Comatose Patients Treated with Therapeutic Hypothermia after Cardiopulmonary Resuscitation**

1. Obtain an EEG early to assess for seizures and treat seizures aggressively.
2. Defer judgment of prognosis for at least 72 hours after the patient returns to normothermia, and preferably for as long as possible.
3. Consider SSEP testing 48 hours after re-establishment of normothermia.
4. Be honest and clear with the patient's family about the clinical impression, uncertainty, and limitations of knowledge.

EEG, electroencephalogram; SSEP, somatosensory evoked potential.

Obtaining EEG early after cardiac arrest may be helpful for patients who were treated with TIMH. One prospective study of 34 patients after TIMH for cardiac arrest showed that a nonreactive EEG background carried a dismal outcome with 0% FPR. Another reason for obtaining EEG early is to guide prompt seizure management. Historically myoclonic status epilepticus (MSE) has reliably predicted poor prognosis, but this may not be the case after treatment with TIMH. In 2009, Rossetti et al reported that in a cohort of 181 patients with cardiac arrest treated with TIMH, 6 patients with postanoxic status epilepticus (PSE)—of whom 2 had MSE—were able to achieve favorable neurologic outcomes as defined by living independently with minor to moderate deficits. These patients were all treated aggressively for their status epilepticus, and all had intact brain stem reflexes, reactive EEG backgrounds, and intact SSEPs. However, of the patients with PSE who recovered to conditions better than persistent vegetative state, MSE was still associated with greater neurologic impairment. Although the sample size of this study was too small to draw statistically meaningful conclusions, its findings cast doubt on MSE as an independent predictor of poor neurologic outcome in patients treated with TIMH.

Bilateral absence of the N20 waves on SSEP likely retains validity as a marker of poor prognosis in patients treated with TIMH. Evidence suggests that although patients treated with TIMH have increased wave latencies, bilateral absence of N20 responses are only found in patients who fail to emerge from coma.

Although there remains controversy regarding the utility of neuron-specific enolase (NSE) levels as prognostic indicators in cardiac arrest patients who have not been treated with hypothermia, it appears that NSE levels are impacted by TIMH. NSE level thresholds that discriminate those with good prognoses from those with poor prognoses have not been definitively established in TIMH-treated survivors. At present, therefore, NSE should not be used to determine prognosis in patients treated with therapeutic hypothermia.

In summary, therapeutic hypothermia makes it more difficult to accurately determine outcome after cardiac arrest. There is insufficient evidence at present to endorse a single test or a specific combination of tests as a reliable means to judge prognosis (Table 69.3). The clinician must be aware that treatment with hypothermia might significantly prolong clearance of medications that confound neurologic assessment.

CAVEATS FOR PROGNOSTICATION

Caution should be exercised when using prognostic algorithms and studies to the comatose patient after cardiac arrest. No method is perfect and none are able to accurately predict outcome for all patients. Any system's ability to predict outcome is limited by differences between the patient in question and the original study population. All studies are subject to statistical realities and the inability to eliminate error completely.

Regarding the generalizability of the preceding algorithms and prognostic tests, it remains a question whether they are valid for younger patients, as studies either did not specify the age range of patients evaluated or enrolled only patients 18 years or older. Hence, none of these predictive rules can be confidently applied to patients younger than 18 years old.

It is important to keep in mind that coma is only one of the many possible sequelae of systemic anoxia and ischemia. Concomitant acute renal failure, liver failure, and shock may impact not only a neurologic recovery but also survival. Preexisting neurologic deficits and the influence of drugs such as paralytics, sedatives, and anticholinergics can also render prognostic indicators invalid. Studies in comatose patients have not addressed the role of these confounders in a systematic fashion. Finally, it must be understood that a *lack* of findings that indicate a poor prognosis does not imply that a good outcome is likely.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 70

Status Epilepticus

Michael L. McGarvey ■ Danielle A. Becker

Status epilepticus (SE) is a medical emergency and is associated with substantial morbidity and mortality. If sustained for more than a few hours, SE may cause neuronal injury as a result of neuronal cell death, gliosis, and network reorganization.

The International League Against Epilepsy and the International Bureau for Epilepsy have defined an *epileptic seizure* as a transient occurrence of signs and symptoms due to abnormal excessive or synchronous neuronal activity in the brain. *Status epilepticus* is defined as a single seizure or multiple seizures in which a patient does not recover consciousness lasting for > 5 minutes. This is based on the observations that 5 minutes represents a fivefold increase in duration over the ~1 minute that a typical seizure lasts as well as the observation that most seizures lasting 5 minutes do not resolve spontaneously.

Although SE is defined by this uniform criterion, the disorder itself has substantial heterogeneity. SE is categorized by its clinical components, its electroencephalographic (EEG) findings, and the patient's clinical history. The first and most important distinction is whether the patient has convulsive (CSE) or nonconvulsive SE (NCSE) (i.e., whether or not the patient has rhythmic jerking or posturing of the arms or legs).

This chapter examines the classification, epidemiology, pathophysiology, management, treatment, and prognosis in adult patients with SE, with particular emphasis on its occurrence in the intensive care unit (ICU).

Epidemiology

The incidence of SE is 10–41/100,000/year in Europe and the United States. SE of focal onset (often followed by secondary generalization) is the most common SE. The major causes of SE in adults are stroke, hypoxia, metabolic derangements, alcohol intoxication, and drug withdrawal. In patients with epilepsy, nonadherence with antiepileptic drug (AED) therapy is the most likely cause. Men are more affected than woman. The estimated direct costs for SE admissions in the United States may be as high as $4 billion per year.

The most common causes of CSE are AED withdrawal or nonadherence to AED therapy in epileptic patients and cerebral vascular disease, whereas alcohol withdrawal, cancer, metabolic disorders, anoxia, poisoning, central nervous system (CNS) infections, and traumatic brain injury (TBI) also contribute. NCSE is likely 25% to 50% of the total incidence of SE although it has been as high as 81% in some series. In critical care patients, 75% to 92% of patients diagnosed with SE are found to be in NCSE as opposed to CSE. In a study of 570 ICU patients with altered mental status who were placed on continuous EEG monitoring (cEEG), 19% had NCSE. The increased availability and utilization of cEEG have undoubtedly increased the clinical team's ability to identify NCSE in patients. The incidences for both CSE and NCSE are considerably higher in those older than 60 years of age.

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As noted earlier, the first and most important distinction is whether the patient has convulsive (CSE) or nonconvulsive SE (NCSE). However, there is an overlap between these two basic classifications as patients may transition between them during their course. For example, in a study of 164 patients treated for CSE with standard therapy and then placed on EEG monitoring, 14.5% of them were found to be in NCSE despite resolution of their convulsions.

CSE by definition requires convulsive movements, defined as rhythmic movements or posturing of the extremities. These movements can be further classified into tonic-clonic, clonic, tonic, and myoclonic CSE. These subtypes are associated with specific EEG correlates at their onset. CSE can then be further subdivided into convulsions consisting of bilateral extremity movement (generalized) versus unilateral extremity or facial movement (partial/focal). Further differentiation is made depending on the patient's level of awareness. In simple CSE, consciousness remains intact, whereas in complex CSE, consciousness is altered. Simple focal CSE and complex focal CSE may also have secondary generalization. If CSE is allowed to persist in any of these subtypes, it is possible that there will be attenuation of the motor symptoms and patients will transition into NCSE (Figure 70.E1).

NCSE is defined as a change in mental status or behavior of at least 30 minutes in duration, without rhythmic motor activity in the extremities, along with an EEG consistent with epileptiform activity. The clinical presentation of NCSE varies extensively among patients and may range from mild confusion to coma. These patients may present with changes in their behavior manifested by increased aggression, crying, inappropriate laughter, or psychosis. When comatose, there may be subtle motor signs such as facial twitching, blinking, nystagmus, eye deviation, or hippus (a rhythmic dilation and contraction of the pupil), which, when present, may be a diagnostic clue.

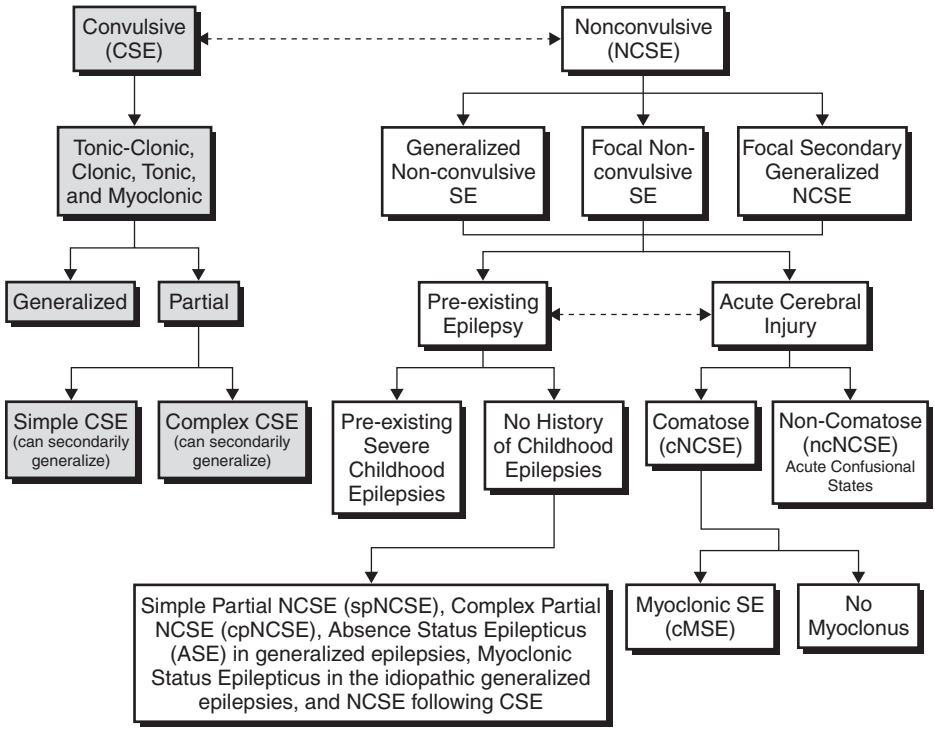


Figure 70.E1 Classification and description of convulsive and nonconvulsive status epilepticus (see the text for more details). CSE, convulsive status epilepticus; NCSE, nonconvulsive status epilepticus.

The diagnosis of NCSE requires the use of EEG, but, even with EEG, it may be difficult to distinguish the subtypes. It is often the case that NCSE goes undiagnosed if EEG monitoring is not employed, particularly in the critical care setting where consciousness is variable due to illness and sedation. Hirsch and colleagues have devised criteria for defining and diagnosing NCSE. These criteria include any pattern lasting greater than 10 seconds (sec) along with the primary criteria of either repetitive generalized focal spikes, sharp waves, spikes and slow waves, or sharp and slow waves at > 3/sec or sequential rhythmic, periodic, or quasi-periodic waves at > 1/sec that gradually increase or decrease in frequency by at least 1/sec. Alternatively, the definition of repetitive generalized focal spikes, sharp waves, spikes and slow waves, or sharp and slow waves < 3/sec with an improvement in clinical state or "normalization" of the EEG pattern acutely following the use of rapidly acting antiepileptic drugs (AEDs) has also been used. Experts in the field still believe there may be scenarios where clinical judgment will take precedent over these criteria in the diagnosis of NCSE but that meeting these criteria is adequate.

Traditionally, NCSE has been initially broken down by age with classifications for the neonatal period, childhood, and adult populations. Discussion of neonatal and childhood NSCE is beyond the scope of this chapter. NCSE in adult patients can be further divided into the following two categories: patients with preexisting epilepsy or patients with acute cerebral injury. There can be overlap between these groups. The group of patients with epilepsy comprises two groups: those with severe epileptic syndromes such as Lennox-Gastaut and other severely disabling childhood epilepsies where the patients have survived into adulthood and those patients with epilepsy but without preexisting childhood encephalopathies. The latter group includes patients with simple partial NCSE (spNCSE), complex partial NCSE (cpNCSE), absence status epilepticus (ASE) in generalized epilepsies, myoclonic status epilepticus in the idiopathic generalized epilepsies, and NCSE following CSE. The spNCSE is an NCSE without loss of consciousness but encompasses a wide spectrum of focal behavioral abnormalities, psychoses, and clinical signs including hallucinations, emotions, and laughter. The cpNCSE is defined as localization-related epilepsy with prolonged continuous or repetitive seizures and alteration of consciousness. The ASE is defined as a sudden but prolonged loss of consciousness without aura, and an EEG that has bilateral synchronous spike and wave discharges at 3/sec. Myoclonic status epilepticus in the idiopathic generalized epilepsies is extremely rare and must be differentiated from myoclonic SE associated with cerebral injury (cMSE). Myoclonic status epilepticus in the idiopathic generalized epilepsies is the nonconvulsive SE associated with patients who are nonencephalopathic but have juvenile absence epilepsy, awakening grand mal epilepsy, or juvenile myoclonic epilepsy.

NCSE in patients with *acute cerebral injury* can be further subdivided into patients who are comatose (cNCSE) or those who are noncomatose but in acute confusional states (ncNCSE). The comatose NCSE group includes a further subdivision differentiating those patients with cMSE or without myoclonus. All these subdivisions of NCSE can be divided into either generalized nonconvulsive SE, focal nonconvulsive SE, or focal secondarily generalized NCSE based on their clinical and electroencephalographic picture (see Figure 70.E1). Different classification symptoms do exist, and it should be noted that the term proper NCSE (pNCSE) denotes all patients who are in NCSE but are noncomatose and does not take into account the presence of acute cerebral injury.

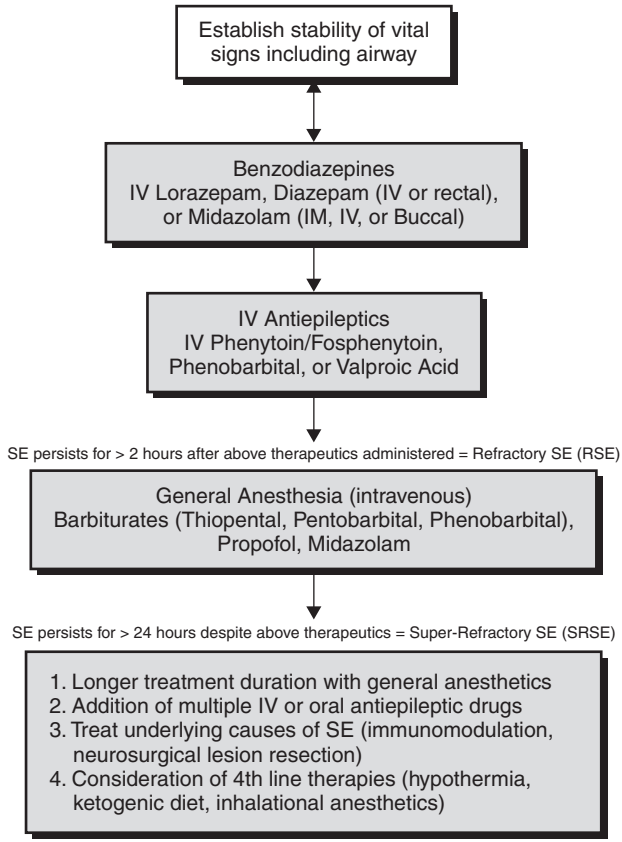


Figure 70.1 Treatment algorithm for status epilepticus. IV, intravenous; IM, intramuscular; SE, status epilepticus.

Approximately 12% to 43% of SE cases fail to respond to first- and second-line therapies. The term *refractory SE* (RSE) is used commonly to describe SE that does not respond to initial dosing with benzodiazepines and at least one antiepileptic drug (Figure 70.1). Half of all patients with RSE have a prior history of epilepsy, but other causes are diverse and include hypoxic-ischemic injury, immune-mediated diseases, infections, toxic-metabolic syndromes, trauma, degenerative disorders, neoplasms, and endocrine disorders.

The term *super-refractory SE* (SRSE) is reserved for patients who continue to have seizures despite the use of general anesthetic agents (see Figure 70.1) to treat their SE or for whom seizures reoccur when therapy is tapered or withdrawn. SRSE may account for up 15% of SE cases. The most common cause of SRSE is acute severe brain injury, but other causes include immunologic, mitochondrial, infectious, toxic, and genetic disorders.

Pathophysiology

Seizures are the result of abnormal electrical discharges of cortical neurons and can arise because of abnormalities at any level in the central nervous system (CNS), from ions, receptors, cells, and networks, to the brain as a whole. Given that an overwhelming majority of seizures end spontaneously, it is hypothesized that an endogenous seizure terminating process must exist in the CNS or

all seizures would be persistent. SE is attributed to a theoretic failure of the CNS's innate ability to terminate an isolated seizure. This failure may occur through two mechanisms: persistence of excessive excitation or loss of normal inhibition. The mechanisms involved may include constant activation of the hippocampus, loss of inhibition by GABAergic interneurons on neurons in the hippocampus with intrinsic pacemaker capability, and increased glutamatergic excitatory synaptic transmission. All of these proposed mechanisms play a central role in epileptogenesis, leading to synchronous, repetitive firing of large populations of neurons. A genetic predisposition may also be involved in SE, shown by a higher incidence of SE in monozygotic than in dizygotic twins.

Neuronal damage is felt to be largely due to excitotoxicity-driven glutamatergic receptor overactivity leading to calcium influx followed by necrosis, apoptosis, and cellular dysfunction, which typically occur after a few hours of SE. Changes in the cellular microenvironment, including hypoxia, acidosis, elevated extracellular potassium levels, and breakdown of the blood-brain barrier, also contribute to neuronal death.

SE leads to widespread systemic effects that occur early and late (> 60 minutes) in its course as a result of its motor and its electrical manifestations. Many of these systemic effects are a result of the catecholamine surge that accompanies SE. Heart rate and blood pressure rise initially, and hypotension develops later. Although there may be increased cerebral blood flow initially in SE, this also declines late in the course, whereas metabolic demands persist, leading to anoxia. Hyperthermia results from tonic muscle contraction and failure of central regulatory mechanisms. A systemic leukocytosis and cerebral spinal fluid pleocytosis occur and sometimes lead to confusion with respect to whether an infectious etiology is causal. Patients can have both a respiratory acidosis and a lactic acidosis, which typically clear once motor seizures are controlled. Electrolyte disturbances, including hyperglycemia, hypoglycemia, hyperkalemia, and hyperphosphatemia, may occur. Aspiration pneumonia and renal failure caused by rhabdomyolysis may also occur.

Management and Therapy

Treatment of SE is aimed at stopping seizures to avoid both systemic and neurologic injury. The immediate goals in the early treatment of SE are the stabilization of vital signs including the airway and identification of the cause of SE along with concurrent early pharmacologic therapy. Glucose should be checked, and if hypoglycemia is present, 100 mg of thiamine should be given followed by appropriate dosing of 50% dextrose.

The first line of treatment for SE is with benzodiazepines, which are $GABA_A$ agonists (see Figure 70.1). This therapy can be started when emergency medical services (EMS) personnel arrive, by families in the field, or upon arrival to emergency departments at medical centers. Treatment with benzodiazepines such as intravenous (IV) lorazepam, diazepam (IV or rectal), or midazolam (IV, intramuscular [IM], or buccal) (depending on availability) is warranted in this setting (see Figure 70.1). Delay in therapy may worsen outcomes.

Lorazepam, which is typically given in up to two (if necessary) 4-mg IV doses, has been shown to be superior to other benzodiazapines because of its long duration of action in the hospital setting. Treatment with benzodiazepines in the field by trained paramedics is safe and results in fewer cardiorespiratory complications. This early treatment has been shown to be effective in stopping seizures in up 55% to 73% of CSE and 15% of NCSE cases. In a randomized, intention to treat, noninferiority study of 893 patients who were treated for SE in the outpatient setting by trained EMS personnel with either IM midazolam to IV lorazepam, IM midazolam was shown to be noninferior to IV lorazepam. There was no difference in safety between the two groups. This trial indicated IM midazolam therapy as a legitimate option in the hyperacute prehospital period alleviating the issue of IV access.

Following this hyperacute therapy, history and physical (including a neurologic) examination should be performed. Cerebral imaging with computed tomography (CT) or magnetic resonance

imaging (MRI) for diagnostic purposes and EEG can be performed based on availability and patient stability. EEG and continuous EEG (cEEG) may be important at this point in identifying NCSE in patients with altered mental status. Lumbar puncture following cerebral imaging may also be indicated to exclude infectious etiologies, particularly in those who are immunosuppressed, febrile, elderly, or with persistent change in consciousness. Appropriate antibiotics and antivirals should be given in this setting until infectious etiologies are excluded. Labs should be sent for AED levels, electrolytes, toxicology screen, and blood counts. In rare cases there are essential antidotes for SE resulting from special causes (e.g., pyridoxine for SE caused by isoniazid toxicity).

If SE persists at this point (after initial benzodiazepine therapy), second-line IV antiepileptic drugs should be initiated. These include IV phenytoin/fosphenytoin, phenobarbital, or valproic acid. If the patient is epileptic and is being treated with one of these medications at baseline, the latter should be the first drug employed.

Phenytoin and fosphenytoin work by slowing the recovery of voltage-gated sodium channels. The IV loading dose of phenytoin is 18 to 20 mg/kg infused at < 50 mg/min (< 25 mg/min in patients at risk for cardiac complications) and maintained at 5 mg/kg/day in three divided doses titrated by free level of the drug. The major drawbacks of IV phenytoin are cardiovascular side effects including hypotension and arrhythmia, which are correlated with infusion rates and IV site soft tissue necrosis resulting from the highly alkaline pK of the drug and its associated vehicle (propylene glycol). It should be avoided in patients with cardiac arrhythmias and in patients having undergone cardiac procedures. These complications are less significant with water-soluble fosphenytoin, which can be infused at a faster rate (18 to 20 mg/kg at 150 mg/min) than phenytoin.

The antiepileptic mechanism of *valproic acid* is modulation of sodium, calcium, and $GABA_A$ channels. Valproic acid is IV loaded at 20 to 40 mg/kg over 10 minutes and maintained at 1000 mg every 6 hours and titrated per blood levels. Valproic acid has fewer cardiovascular side effects than phenytoin but has been associated with hyperammonemia, thrombocytopenia, and hepatic and renal dysfunction. It should be avoided in patients with liver, renal, pancreatic, and mitochondrial disorders. There are a few small clinical trials indicating that valproic acid may have some benefit over phenytoin in the treatment of prolonged SE.

Phenobarbital had been used historically in the setting of prolonged SE, although it is rarely used in this setting now because of its adverse cardiovascular effects, long infusion rate, and long half-life. Its use should be reserved when other drugs are contraindicated. The IV loading dose of phenobarbital is 20 mg/kg at an infusion rate of < 60 mg/min, maintained at 1 to 3 mg/kg/day in three divided doses and titrated to blood level. In general, the addition of a second line IV AED as discussed earlier likely only resolves seizures in an additional 10% of SE cases.

If seizures continue for > 2 hours after the second line of therapy is initiated, patients have entered into refractory SE (RSE). General anesthetics are typically administered at this point with a goal to place the patient into a burst suppression by EEG (interburst interval of 10 sec) at a level where all seizure activity is controlled. This is to prevent excitotoxicity by suppressing all electroencephalographic activity and to avoid neural injury. These patients require ICU monitoring. Use of general IV anesthetics requires the use of assisted ventilation and typically the use of vasopressor agents and cardiovascular monitoring given the cardiorespiratory depression associated with their use. The initial choices for continuous IV anesthetic therapy in this setting include barbiturates (thiopental, pentobarbital, and phenobarbital), propofol, and midazolam, which are all effective and intrinsic antiepileptics because of their ability to modulate $GABA_A$ receptors. Barbiturate anesthesia, although very effective, has major drawbacks associated with its use including a long half-life resulting in long recovery times (even with short infusion times), liver metabolism resulting in drug interaction and auto-induction, and almost certain cardiorespiratory depression. *Pentobarbital* is loaded at 5 mg/kg IV boluses, up to 50 mg/min, until seizures

are controlled and then maintained at 1 to 5 mg/h. *Thiopental* is similarly loaded with 2 mg/kg IV boluses and maintained at 3 to 5 mg/kg/h.

Midazolam is a short-acting benzodiazepine whose major advantage includes a lack of accumulation in fatty tissues, thus leading to a theoretically shorter half-life. Unfortunately, if midazolam is given for prolonged periods, its pharmacokinetics change to resemble other longer-acting benzodiazepines, such as lorazepam, with prolonged recovery times when stopped. Although midazolam has only moderate cardiorespiratory depressant effects, it has a strong tendency for tolerance, and seizure recurrence is common with prolonged use. Midazolam is loaded at 0.2 mg/kg IV and maintained at 0.1 to 0.6 mg/kg/h.

Propofol has the advantages of both rapid onset and recovery time even with prolonged use and less cardiorespiratory suppression than midazolam or barbiturates. Its major drawback is the risk of propofol infusion syndrome, which, although rare, is potentially lethal because of a combination of metabolic acidosis, lactic acidosis, rhabdomyolysis, cardiac instability, renal failure, hyperlipidemia, and hyperkalemia. Propofol is loaded at 2 mg/kg IV and maintained at 2 to 10 mg/kg/h.

In a meta-analysis of these three therapies for the treatment of RSE, no significant benefit of any one therapy could be identified. A trial of general anesthesia for 24 to 48 hours should be attempted and then first followed by a slow wean of medication over a 24-hour period. If there is recurrence of SE, longer periods of IV anesthesia can be considered with even more prolonged weaning of medications.

If SE persists or recurs for > 24 hours after general IV anesthesia, the patient is termed to be in SRSE. This includes reoccurrence of seizures when therapy is tapered or withdrawn. At this point, neuronal injury has likely already begun as a result of excitotoxicity so additional therapies are aimed at neuroprotection and prevention of systemic complications caused by prolonged anesthesia. It is common in SRSE to add more IV or oral AEDs to the standard therapies for RSE in hopes that drugs with different mechanisms of actions will have an impact on the SE. It is unclear what beneficial effects this practice has because of a lack of controlled data, but there have been case reports demonstrating successful treatment. This list would include every AED that has been approved for the treatment of epilepsy. The most promising add-on or alternate AED therapies include levetiracetam, lacosamide, and topiramate.

Although there is a lack of data and experience, several secondary therapies exist to treat SRSE. *Ketamine* is an *N*-methyl-D-aspartate (NMDA)-receptor antagonist that has been used effectively in several case reports of prolonged SRSE and even rarely in early RSE. The major advantage of ketamine is that it has little to no cardiodepressing effects. Inhaled anesthetics such as isoflurane have been employed with moderate success, but their use has been limited by high complication rates and logistical difficulty in using them outside of the operating room. IV magnesium sulfate is the drug of choice for treating seizures caused by eclampsia and should likely be the first-line drug for treating SE resulting from eclampsia. Although magnesium sulfate has never been demonstrated to be effective, it has been used in SRSE because of its safety profile. Corticosteroids have been used in SRSE in the past for consequences associated with cerebral edema and more recently with the discovery of SE related to encephalitis resulting from antibody associated autoimmune disorders such as anti-NMDA receptor antibodies. Steroids, plasmapheresis, IV immunoglobulin (IVIG), and cyclophosphamide have been used to treat the underlying disorder to abolish seizures in these patients. The ketogenic diet, therapeutic hypothermia, neurosurgical resection of lesion or focus detected on imaging, and electrical or magnetic stimulation have also been employed in extreme circumstances (see Figure 70.1).

There are special circumstances in the critically ill that have led to a need to modify the management of SE, some of which have already been discussed. Patients with liver failure will have an increase in AED drug levels, which are hepatically metabolized and may suffer from hypoalbuminemia leading to higher levels of protein-bound drugs, such as is the case for

BOX 70.1 ■ Medications and Other Interventions Relevant to Patients in Intensive Care Units That Have the Potential to Lower Seizure Thresholds

Medications

Analgesics: meperidine, fentanyl, tramadol
Antiarrhythmics: mexiletine, lidocaine, digoxin
Antibiotics: β-lactams, quinolones, metronidazole, isoniazid
Calcineurin inhibitors
Antidepressants: bupropion and maprotiline
Neuroleptics: haloperidol, clozapine, phenothiazines
Chemotherapy agents: ifosfamide, cisplatin, methotrexate
AEDs: tiagabine
Antiviral agents: acyclovir, valacyclovir, ganciclovir, foscarnet, vidarabine
Miscellaneous: baclofen, amphetamines, and theophylline

Nonmedications

Hyperventilation
Severe alkalemia (i.e., pH > 7.50 to 7.55)

phenytoin (see also Chapter 17). In this particular setting, nonprotein bound, nonhepatically metabolized AEDs such as levetiracetam, pregabalin, and gabapentin may need to be considered despite a lack of established efficacy or experience with their use in SE. Renal failure also results in hypoalbuminemia and difficulty eliminating renal extracted medications. Levetiracetam, gabapentin, pregabalin, topiramate, and pentobarbital may need to be given at lower doses and dosed following dialysis. Special care should be given to follow the drug levels of patients who are on highly protein bound medications such as phenytoin, valproic acid, and benzodiazepines and who are on dialysis, particularly those on continuous dialysis.

In the critical care setting, a large number of medications are utilized that have the potential to lower seizure threshold. It is important to recognize these medications and use caution when administering them to patients with epilepsy or known SE (Box 70.1).

Prognosis and Outcomes

Reported case fatality rates for SE vary widely from 1.9% to 80% depending on age, etiology, sex, and classification of SE. SE may also carry a long-term case fatality risk that is three times as high as the general population 10 years after the patient's initial episode of SE. Much of the mortality associated with SE is thought to be associated with the underlying cause of the SE. Stroke, hypoxia, CNS infections, and metabolic disorders are particularly devastating with case fatality rates up to 80%. It is unclear how much of the mortality and morbidity is attributable to SE alone. CSE carries a mortality of ~20% in those who are elderly, anoxic, or have longer seizure duration.

The development of RSE leads to a mortality approaching 40%, but it is substantially influenced by etiology, with those with acute brain pathology having poorer outcomes than those with other etiologies. The duration of SE may have an impact on mortality with those being treated successfully in the first 30 minutes having a mortality rate of < 3%, and those whose successful treatment was delayed by up to 6 hours having a progressively worse outcome. The presence of SE after a cardiac or respiratory arrest has been associated with a mortality of ~70%. CNCSE or cMSE following cardiac arrest, even when therapeutic hypothermia (TH) has been performed, has been associated with very poor outcomes with patients experiencing death or persistent vegetative states at rates approaching 100%. However, there have been reports of rare cases of good outcomes in survivors who developed cNCSE or cMSE following cardiac arrest.

The cNCSE and cMSE detected in this setting may be a totally separate disorder with electrical patterns detected in these patients representing the dying brain and not an SE that is amenable to treatment.

Even following successful treatment of seizures in SE, surviving patients can be left with persistent disability and require long-term care. However, it is unclear in these cases whether SE itself may have any impact on outcome independently or if disability was secondary to an underlying etiology of the SE. In a study of 248 patients presenting with CSE, 19% of the patients died, but an additional 39% had functional disability at 90 days. These poor functional outcomes were associated with age, stroke, refractory status, and length of SE. The fact that RSE and the length of SE affect outcomes may imply that more aggressive treatment of SE may have a beneficial effect on outcomes. An episode of prolonged SE may predispose patients to developing epilepsy. In a study that compared 95 patients who presented with SE as their first seizure with 317 patients whose first seizure was brief and not defined as SE, there was a 3.3-fold increase in the risk of recurrent seizure even after controlling for age, sex, and cause of the seizure in those who presented with SE. Patients with RSE have longer hospitalizations and increased disability compared to non-RSE patients.

It is also unclear what effect the presence of NCSE has on outcome, particularly in the comatose NCSE subgroup. There are clear differences in the outcomes for noncomatose NCSE and comatose NCSE patients, with those in the latter group having much poorer outcomes.

Although cardiac arrest is the most common cause of death in the United States, improved resuscitation techniques and the implementation of standardized protocols including therapeutic hypothermia (TH) have led to significant improvements in outcomes. In general (see Chapter 49 for details and exceptions), mild therapeutic hypothermia to 32.0° to 34.0° C is recommended in the resuscitated, unconscious patient who has suffered a cardiac arrest. Neurologic outcomes in these patients vary on a continuum from normal to coma. It is clear that NCSE often occurs following cardiac arrest and that NCSE can cause coma. It is unclear if patients who are postcardiac arrest suffer from coma as a result of NCSE in and of itself or whether TH can be an effective therapy for postcardiac arrest NCSE. A series of 101 patients undergoing TH following out-of-hospital cardiac arrests were placed on cEEG. Thirty of these patients awoke (29/30 survived, with four making good recoveries). Twelve patients developed NCSE (3 patients were in NCSE at the onset of cEEG). Most seizures began within 12 hours following cardiac arrest. Only 1 of the patients with NCSE survived in a vegetative state, although another did arouse but eventually died from multiorgan failure. Twenty-one of the patients developed myoclonic SE, and none of these patients survived or regained consciousness. Patients with NCSE or myotonic SE were significantly less likely to survive. As noted earlier, myotonic SE must be distinguished from postarrest syndrome of diffuse intentional clinical myoclonus, as patients without seizure activity on their EEG may have better clinical outcomes following cardiac arrest and coma.

The issue as to whether to treat refractory NCSE, particularly comatose NCSE, resulting from acute brain injury has been debated. The answer to this question is based on several factors including poor outcomes associated with NCSE, whether NCSE is actually causing harm, and the side effects of prolonged treatment with IV general anesthetics. This issue requires additional research, and treatment at this time is based on the best clinical judgment of the treating team and the personal preferences of patients as expressed in their advance directives or by their surrogate decision makers (see Chapter 102).

An annotated bibliography can be found at www.expertconsult.com.

Patients with comatose NCSE clearly have worse underlying etiologies for their NSCE. It remains in question whether NCSE has an overall effect on outcome or if the underlying cause is the driving force for morbidity and mortality in these patients. In a retrospective study of 50 patients who presented with NCSE, 32 patients had pNCSE and 18 had cNCSE. Only 2 of the patients died in the pNCSE group (1 patient with sporadic Creutzfeldt-Jakob disease and another with progressive myoclonus epilepsy [Lafora type]). Twenty of the patients had a previous diagnosis of epilepsy in the pNCSE group. Only 6 of the patients in the pNCSE group required ICU level treatment for refractory NCSE. In the cNCSE group, only 1 patient had a previous history of epilepsy. Fifteen were diagnosed while in the ICU from EEG that was performed because of coma. Six patients had strokes, 4 had cerebral anoxia, 3 had a central nervous system infection, 2 had subdural hematomas, 2 had CSE, and 1 was diagnosed with sepsis. Eleven of the patients died with only 2 of these patients having good outcomes.

The diagnostic evaluation and treatment of SE have evolved over time. With the help of cEEG monitoring and new antiepileptic therapies, patients in NCSE are being identified earlier and treated more aggressively. The longer the SE is sustained, the greater the potential to cause systemic and neuronal damage. Episodes of prolonged SE likely predispose patients to developing epilepsy, and in those who already have a diagnosis of epilepsy, it may increase complications, as well as morbidity and mortality.

Refractory status epilepticus (RSE) and longer duration of SE are associated with worse outcomes and suggest that more aggressive treatment of SE may have a beneficial effect on outcomes. However, even following successful treatment of seizures in patients in SE, surviving patients often have persistent disability and require long-term care. Thus, the diagnostic evaluation and treatment of SE remains a critical issue. The goal for ICU clinicians is to diagnose and treat SE sooner, in hopes of improving the morbidity and mortality associated with SE.

It remains unclear if SE itself has any impact on outcome independently or if the resulting disability is secondary to the underlying etiology of the SE. Nevertheless, poor functional outcomes and worsened cognitive impairment have been associated with RSE, SRSE, and the overall length of time a patient is in SE. Modification of the previous definition of SE as lasting > 30 minutes to SE lasting > 5 minutes was one of the first steps taken toward more aggressive identification and treatment. The second step was the increased availability and utilization of cEEG monitoring, which has also increased the ICU team's ability to identify NCSE in patients. EEG and cEEG play a crucial role in identifying NCSE in patients with altered mental status and who were otherwise not diagnosed as being in SE because of a lack of convulsive movements. The longer the patient is in SE, the more likely he or she will go into RSE. Patients in RSE and SRSE have longer hospitalizations and increased disability compared to non-RSE patients.

The treatment algorithm set forth in this chapter (see Figure 70.1) is important to follow because it is aimed at stopping seizures as quickly and safely as possible to avoid both systemic and neurologic injury. The management and treatment for SE have changed over the years. Medication such as phenobarbital, which had been used historically in this setting, is now rarely used because of its cardiovascular suppressive effects, long infusion rate, and long half-life. If SE continues for > 2 hours after the second line of IV antiepileptics is initiated (i.e., patients would then be considered to be in refractory status), general anesthetics are typically given along with cEEG monitoring. A patient who is still in SE 24 hours after the onset of general IV anesthesia has progressed to SRSE and neuronal injury has likely begun. At this point, alternative therapies should be employed, aimed at neuroprotection and prevention of systemic complications.

In addition, there are special circumstances, such as liver or renal failure in ICU patients in SE, that have led to a need to modify the management of SE with nontraditional AEDs despite a lack of established efficacy or experience with their use in SE. It is unclear how beneficial these practices are due to a lack of controlled clinical trials, but case reports have demonstrated successful outcomes. Thus, although treatment algorithms have come a long way, there are still gaps in supporting data.

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CHAPTER 71

Stroke

Ramani Balu ■ Scott E. Kasner

Despite advances in understanding and treatment, stroke remains the fourth leading cause of death in the United States, claiming 150,000 lives annually. Depending on size, type, and location, acute strokes are often medical emergencies requiring intensive care unit (ICU) monitoring and care of life-threatening complications. This chapter provides an overview of the acute management of critically ill stroke patients. Other topics such as secondary stroke prevention, although important, are not discussed here, as they do not directly pertain to initial acute patient care.

Definitions and Classification of Strokes

Stroke is broadly defined as the abrupt onset of persistent neurologic symptoms caused by inadequate blood flow to a particular area of the brain or by hemorrhage into the brain, which compresses brain tissue and secondarily compromises perfusion. *Ischemic strokes*—which are caused by inadequate blood flow to the brain—constitute ~80% of all strokes and can be caused by a variety of mechanisms, including large artery atherothromboembolic disease, small artery disease, cardioembolism, or less common causes including hypercoagulable states, cocaine abuse, arterial dissection, and hypoperfusion. A *transient ischemic attack* (TIA) is a temporary focal neurologic deficit caused by an abrupt decrease in cerebral blood flow that does not cause permanent infarction. TIA and ischemic stroke represent two points along a continuum of acute ischemic cerebrovascular disease (analogous to unstable angina and myocardial infarction in coronary artery disease) and are therefore managed similarly in the acute setting. Patients with a single TIA, however, are unlikely to be admitted to an ICU.

Hemorrhagic strokes—which are caused by abrupt bleeding into the brain—make up the remaining 20% of strokes and can be further divided into primary intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). ICH most commonly results from hypertension (which usually results in deep subcortical, brain stem, and cerebellar hemorrhage), cerebral amyloid angiopathy (CAA, which results in predominantly superficial and lobar hemorrhage), rupture of an arteriovenous malformations (AVM), or as a complication of systemic anticoagulation (for example, supratherapeutic dosing of warfarin). In contrast, SAH is generally caused by a ruptured aneurysm. Ischemic strokes can often have *hemorrhagic transformation*, because infarcted tissue is friable and susceptible to bleeding; however, hemorrhagic transformation is more appropriately thought of as a potential complication of ischemic stroke, rather than a subtype of hemorrhagic stroke.

STROKE MIMICS

Other neurologic and systemic conditions can cause abrupt neurologic deficits that may be difficult to distinguish from acute stroke. *Migraine headaches* can be associated with transient

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focal neurologic symptoms preceding or during the early phase of the headache. Rarely, these deficits may persist and result in frank infarction. *Focal seizures* may manifest with deficits such as aphasia, focal weakness, or sensory symptoms that can mimic a stroke. In addition, postictal neurologic deficits (Todd's paralysis) may persist for greater than 24 hours after a seizure. Finally, global metabolic stress (for example, marked hyperglycemia, acidosis, or electrolyte disturbance) can cause focal neurologic deficits. This likely occurs because the metabolic stress unmasks preexisting focal neurologic damage (such as a prior stroke from which the patient has recovered).

Initial Diagnosis and Management

The initial diagnosis and management of stroke patients typically occur in the emergency department. Because different stroke types have markedly divergent management strategies and potential acute treatments (such as thrombolysis using intravenous [IV] tissue plasminogen activator, described later) that can only be given within a short time window, a directed approach is required when evaluating patients who present with acute neurologic deficits (Figures 71.1 to 71.3). A clear history of the time of symptom onset is needed to determine whether the patient may be eligible for thrombolysis. If the patient or family members cannot provide an exact time when symptoms occurred, the time when the patient was last seen normal is assumed to be the time of symptom onset. Certain historical features may help distinguish stroke subtypes. For example, sudden-onset "thunderclap" headache, neck stiffness, and nausea that coincide with neurologic symptom onset strongly suggest SAH (although headache is often nonspecific and does not reliably distinguish ischemic from hemorrhagic stroke). In contrast, symptoms that develop over minutes are more likely to be associated with ICH.

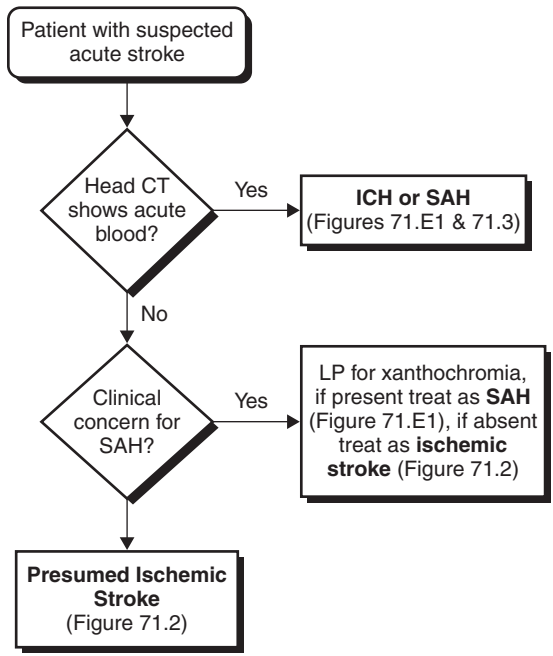


Figure 71.1 Clinical decision pathway for patients with suspected acute stroke. A noncontrast head CT is used to differentiate between ischemic and hemorrhagic strokes.

A brief, directed neurologic examination helps to localize the lesion and quantify the extent of neurologic impairment. Aphasia, neglect, and forced gaze deviation away from the hemiparetic side suggest *cortical* involvement. Pure motor hemiparesis or hemisensory loss affecting the face, arm, and leg equally occur with *subcortical* injury. Finally, "crossed signs" (such as ipsilateral facial weakness and contralateral arm and leg weakness), cranial nerve abnormalities, and ataxia localize to the *posterior fossa* (brain stem and cerebellum). The NIH Stroke Scale (NIHSS) (see stroke.nih.gov/documents/NIH_Stroke_Scale.pdf for description) provides a quick, reliable metric to measure of extent and severity of neurologic injury and can be used to track clinical changes over time.

Laboratory blood work, including electrolytes, renal function panel, complete blood count, coagulation panel, and troponin, should be obtained on presentation to help identify (1) metabolic stressors that may mimic stroke, (2) coagulopathies that may contribute to intracerebral hemorrhage, and (3) acute cardiac ischemia that can lead to cardioembolism. An electrocardiogram (ECG) is indicated to identify cardiac ischemia and rhythm disturbances (such as atrial fibrillation), both of which can cause cardioembolic strokes.

After a clinical diagnosis of acute stroke has been made, it is imperative to distinguish hemorrhagic from ischemic stroke as rapidly as possible and initiate appropriate therapy. A computed tomographic (CT) scan is usually the first neuroimaging study to be performed because it is readily available and highly sensitive for acute bleeds (see Figures 71.1 to 71.3 and Figure 71.E1). Intraparenchymal or intraventricular hyperdense lesions suggest ICH, whereas hyperdensities within the sulci and basal cisterns imply SAH. In the absence of evidence for hemorrhage, an ischemic infarct is presumed because radiologic signs of cerebral ischemia may be subtle or undetectable

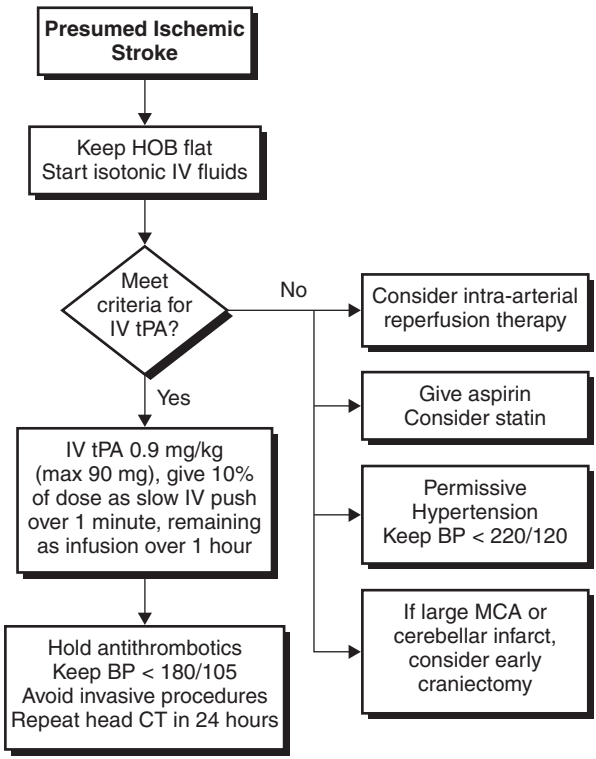


Figure 71.2 Clinical decision pathway for management of acute ischemic stroke. Patients that meet the criteria should be given intravenous tPA for acute reperfusion.

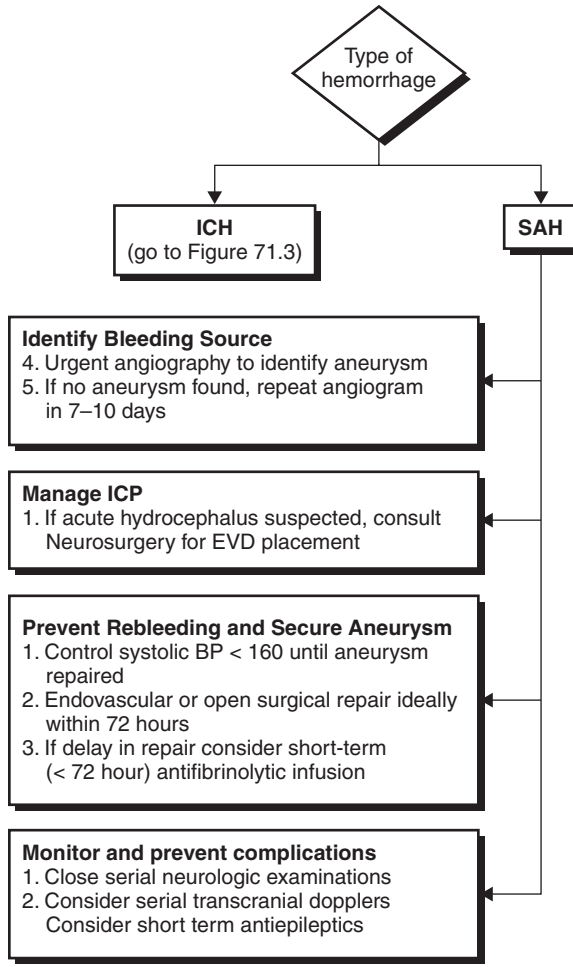


Figure 71.E1 Clinical decision pathway for management of subarachnoid hemorrhage.

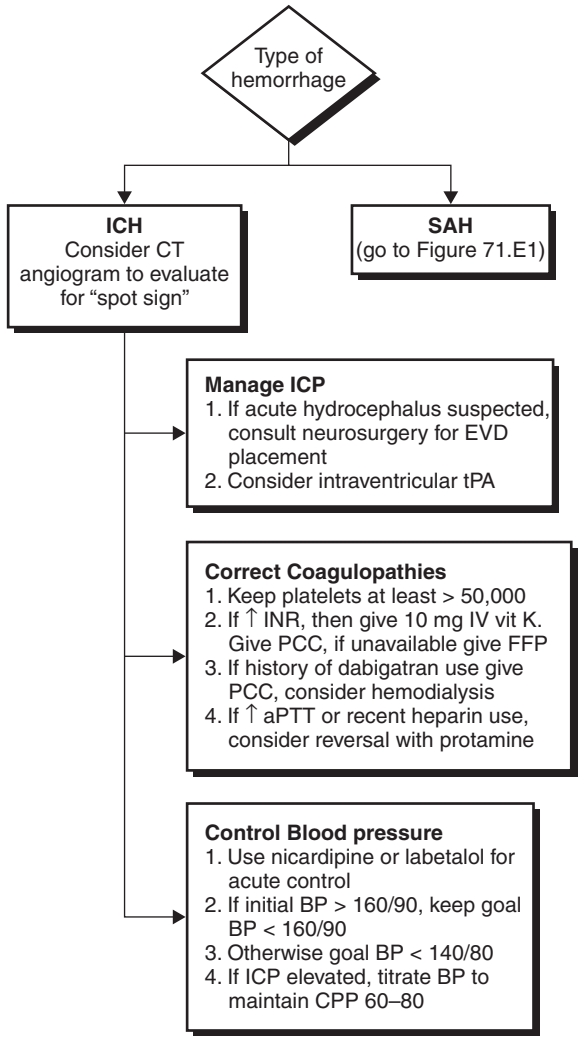


Figure 71.3 Clinical decision pathway for management of acute intracerebral hemorrhage. CT angiogram to evaluate for a "spot sign" should be considered in patients with ICH. EVD, externalized ventricular drain; ICP, intracranial pressure; INR, international normalized ratio; FFP, fresh frozen plasma; aPTT, activated partial thromboplastin time; PCC, prothrombin complex concentrate.

within the first 12 hours. It is important to realize, however, that CT can miss a small proportion of SAH (< 5%). Thus, if clinical suspicion for SAH is high, a negative CT should prompt further testing with lumbar puncture to look for red blood cells or xanthochromia (yellowish discoloration of CSF) or with a magnetic resonance imaging (MRI) scan.

Management of Ischemic Stroke

ACUTE REPERFUSION STRATEGIES

Multiple double-blinded randomized controlled trials have shown that thrombolysis and reperfusion using alteplase, also called tissue plasminogen activator (tPA), can significantly improve

outcome when given early to patients with ischemic stroke (Figure 71.2). In these trials, patients treated with IV tPA within 3 hours of symptom onset had significant improvement in neurologic outcome at 3 months. These benefits were independent of the type of ischemic stroke. Subsequent trials and new guidelines extended the time window for tPA usage to within 4.5 hours of symptom onset.

If patients have risk factors for systemic bleeding (such as systemic anticoagulation, recent major surgery, recent gastrointestinal or urinary tract hemorrhage, prior arterial puncture at a noncompressible site within 7 days, or evidence of a coagulopathy), then tPA should not be administered. tPA is also contraindicated if there is evidence of intracerebral or subarachnoid hemorrhage, if blood pressure is elevated (systolic blood pressure [SBP] > 185 mm Hg or diastolic blood pressure [DBP] > 110 mm Hg), as elevated blood pressure can increase the risk of hemorrhagic transformation, or if serum glucose is < 50 or > 400 mg/dL as these conditions can cause focal neurologic signs that mimic stroke. The full list of eligibility criteria can be found in the American Heart Association (AHA) guidelines for the management of acute ischemic stroke (see references).

Antithrombotic drugs should be withheld for 24 hours after tPA infusion to limit hemorrhagic transformation. Blood pressure must be maintained below SBP 180 and DBP 105 mm Hg for the first 24 hours after tPA. A head CT should be obtained at ~24 hours after infusion to detect possible hemorrhagic transformation. If no bleeding occurs, then antiplatelet agents and antithrombotic agents can be started. Invasive procedures (such as Foley catheter or central venous catheter placement) should be avoided in the first 24 hours to minimize other bleeding complications.

Patients who do not present within the 4.5-hour window for IV tPA or who have systemic contraindications may be candidates for *intra-arterial therapies*. One study showed that catheter-directed, local, intra-arterial infusion of a thrombolytic agent in patients with angiographically documented proximal middle cerebral artery (MCA) occlusion resulted in improved functional outcome if given within *6 hours of symptom onset* compared to patients who did not receive this therapy. The specific thrombolytic agent used in this trial is not commercially available, but tPA is used in many centers for this purpose based on indirect evidence. Other interventional therapies for mechanical clot extraction with or without thrombolytic drugs have also been developed. Although promising, these intra-arterial therapies remain investigational and further studies are required before they enter into routine clinical use. Most notably, a trial showed that IV tPA plus intra-arterial intervention was not more effective than IV tPA alone.

SUPPORTIVE THERAPY

Most patients who present with ischemic stroke unfortunately are unable to receive acute thrombolysis because of the narrow time window and other selection criteria. In these patients, care is directed at aggressively preventing stroke progression and limiting other medical complications (see Figure 71.2). The occlusion of a cerebral artery produces a core of nonviable brain tissue that is surrounded by a zone of viable but at-risk tissue known as the *penumbra*. Maximizing blood flow to the penumbra while limiting the core infarct area is a central principle of medical management of ischemic stroke.

Antiplatelet agents such as aspirin provide a small but significant mortality benefit and decrease acute recurrent stroke risk and should be administered early (within 24 hours) after ischemic stroke onset. Statins may also have an acute benefit through unclear mechanisms (possibly by limiting the extent of inflammatory injury). Systemic anticoagulation (for example, with IV unfractionated heparin) should in general be avoided, as studies suggest that the risk of hemorrhagic transformation outweighs the benefit of recurrent stroke prevention in the first few days after stroke onset. Anticoagulation may be useful in certain circumstances, for example, in patients with fluctuating symptoms (implying an unstable thrombus) or in the setting of arterial dissection, but these areas remain highly controversial.

Metabolic stresses such as fever and hyperglycemia should be aggressively controlled. Fever is common in stroke patients, and multiple cohort studies have demonstrated markedly worse outcomes (increased infarct size, neurologic disability, and mortality) in febrile patients: the likelihood of death or disability increases twofold for every 1° Celsius above normal. Acetaminophen can be used to limit fever responses. Other methods using surface and intravascular conductive devices to maintain normothermia have been developed; however, the impact of these interventions on outcome is not clear.

Similar to fever, multiple studies showed a relationship between admission hyperglycemia and worsened neurologic outcome. A multicenter randomized controlled trial of intensive glycemic management in ischemic stroke patients is currently under way. In the meantime, it is reasonable to control blood sugar in a similar fashion to other critically ill medical patients (see Chapter 12).

Blood Pressure Management and Optimization of Cerebral Blood Flow

Under normal conditions, cerebral blood flow (CBF) is maintained at a relatively constant level despite fluctuations in systemic blood pressure through autoregulation of cerebrovascular resistance. When mean arterial pressure (MAP) increases, cerebral arterioles normally constrict. Conversely, there is a compensatory dilation of the cerebral vasculature in response to hypotension. After stroke, autoregulation is impaired and blood flow varies linearly with changes in MAP. Thus, small changes in blood pressure can have a profound impact on CBF and infarct progression.

Patients with ischemic stroke are often hypertensive on presentation. This hypertensive response generally abates over the course of 7 to 10 days and likely reflects a reflex that maintains blood flow in the setting of impaired cerebral autoregulation. Aggressive blood pressure lowering should therefore be avoided and in general the head of the bed should be kept flat to optimize cerebral blood flow. Similarly, prolonged hypotension should prompt a thorough search for potential causes (such as sepsis, hypovolemia, myocardial infarction causing cardiogenic shock, or hemopericardium causing tamponade after thrombolytic therapy). Although markedly increased blood pressure can increase the likelihood of hemorrhagic transformation, current guidelines support allowing blood pressures of up to SBP ≤ 220 mm Hg and DBP ≤ 120 mm Hg in the acute setting. If blood pressure increases above these values, bolus doses of IV labetalol or a continuous infusion of IV nicardipine can be used to effect a modest (up to 15%) reduction. In practice, outpatient blood pressure medications are often held unless there are signs of end-organ damage from hypertension, and volume expansion with isotonic crystalloid fluids is given to maximize the permissive hypertensive response and cerebral blood flow. The exception to this principle is in patients who have received IV tPA. In these patients, the risk for hemorrhagic transformation after thrombolysis is high and blood pressure should be maintained at SBP ≤ 180 mm Hg and DBP ≤ 105 mm Hg. Patients with aortic dissection or acute myocardial ischemia should also have their blood pressure lowered accordingly.

Pharmacologically induced hypertension has been used in ischemic stroke patients who have neurologic symptoms that appear perfusional (for example, hemiparesis that worsens with decreased blood pressure). Small observational studies showed that induced hypertension (with phenylephrine, for example) can increase CBF and may improve neurologic symptoms, although other studies have yielded conflicting results. This approach cannot be recommended in routine care at present but may be worthy of consideration for patients who clearly worsen when their blood pressure declines.

Management of Cerebral Edema

Acute ischemic strokes result in cytotoxic edema, which can cause compression of adjacent neural structures, midline shift, and potentially life-threatening herniation. The risk of malignant edema and herniation is greatest in patients with cerebellar and complete middle cerebral artery (MCA) territory strokes. These patients require vigilant clinical monitoring to look for signs of infarct

progression and clinical deterioration. Key clinical signs include otherwise unexplained agitation, depression of consciousness, pupillary dilatation on the side of the infarction (caused by compression of the midbrain and oculomotor nerve from uncal herniation), weakness of the leg on the same side as the infracted hemisphere (which can be caused by either uncal or subfalcine herniation), or vital sign instability (such as bradycardia and hypertension, which, along with respiratory instability comprises *Cushing's triad* and heralds tonsillar herniation). It is important to note, however, that sudden onset tachycardia or hypotension can also herald herniation. In general, intracranial pressure (ICP) monitors (such as an intraventricular catheter or subdural bolt) are not useful because the measured global intracranial pressure may not reflect local pressure gradients between the infarct and surrounding tissue. Previous studies have shown that clinical signs of herniation often precede increases in intracranial pressure in patients with large ischemic infarcts who have ICP monitors.

Acute therapies such as hyperventilation or infusion of hyperosmolar solutions (such as mannitol or hypertonic saline) may reduce edema and improve clinical symptoms; however, these measures are temporizing and do not change the overall clinical course. Furthermore, they may worsen outcomes: (1) by causing cerebral vasoconstriction, hyperventilation decreases perfusion to the entire brain and can actually worsen ischemic injury; (2) osmolar therapies may draw free water preferentially out of normal brain where the blood-brain barrier is intact and draw it into infarcted brain, paradoxically worsening the local edema. Patients with malignant edema should therefore be considered for decompressive craniectomy and duraplasty, which allows for herniation of infarcted brain tissue out of the craniectomy site instead of into adjacent brain structures (Figure 71.E2). Suboccipital craniectomy is a widely accepted life-saving procedure for edema associated with large cerebellar infarcts. Similarly, malignant cerebral edema from an MCA territory infarction can be definitively treated by decompressive hemicraniectomy. Three randomized controlled trials have shown a mortality benefit for patients with malignant edema from MCA territory strokes who receive early (within 48 hours) hemicraniectomy. Many of the patients who survived, however, had significant functional disability after surgery, likely reflecting the extensive size of infarction.

Management of Intracerebral Hemorrhage

The principles of ICH management involve management of intracranial pressure (ICP), correction of underlying coagulopathies that may exacerbate bleeding, aggressive blood pressure control to limit hematoma expansion, and prevention of other medical complications (Figure 71.3). These interventions are typically pursued in tandem. Surgical clot removal has not been shown to improve overall clinical outcome but may be beneficial in patients with large, superficial hemorrhages. Despite aggressive efforts, mortality from ICH is high. Scoring systems have been devised to calculate in-hospital mortality risk and functional outcome based on patient age, initial neurologic examination, hematoma size, and site of bleeding. It is, however, important to use these scores judiciously when making treatment decisions, as they may lead to a self-fulfilling prophecy.

PREDICTORS OF HEMATOMA EXPANSION

Approximately 40% of all ICHs will expand from their initial size within 24 hours of presentation. Hematoma expansion is associated with worse clinical outcomes; identifying factors that contribute to hematoma expansion are thus crucial to direct acute patient care. Disruption of the coagulation cascade (either secondary to medications such as warfarin or from intrinsic coagulopathies), elevated blood pressure, and poorly controlled diabetes are all associated with increased hematoma size. However, it continues to be difficult to predict which patients will have significant hematoma expansion based on clinical characteristics alone. Studies have used

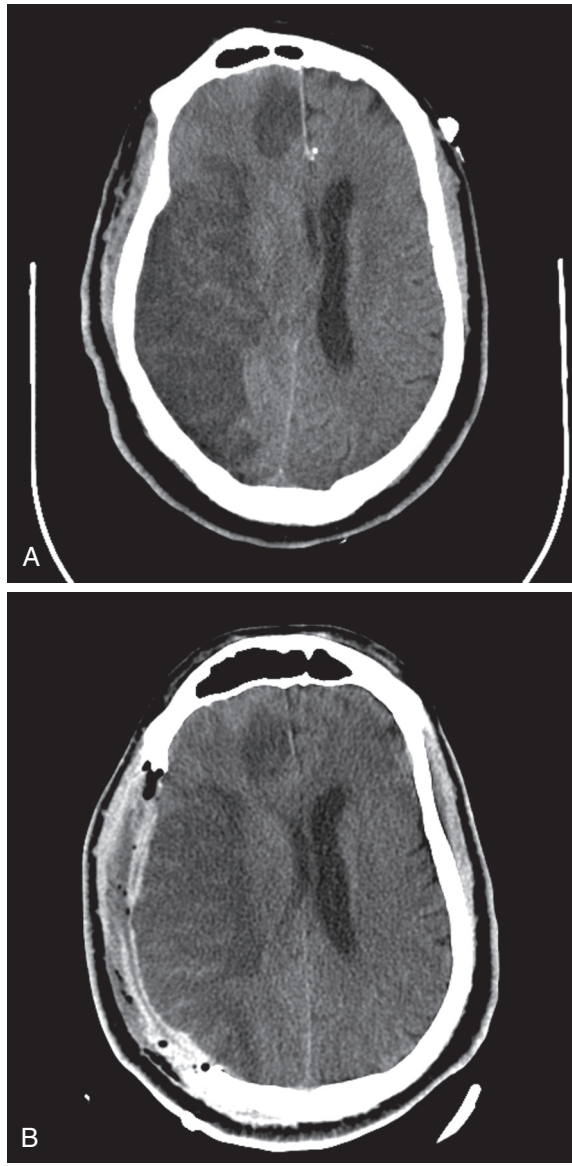


Figure 71.E2 **A** and **B,** malignant MCA and ACA territory infarction. Note shift of right hemispheric contents across midline. Panel **B** shows CT scan after decompressive hemicraniectomy. The infarcted brain tissue is now herniating out of the craniectomy site and the midline shift has improved. Note the areas of curvilinear hyperintensity within the infarction that represent areas of hemorrhagic transformation.

contrast-enhanced CT angiography to identify patients at risk for hematoma expansion. The presence of a "spot sign" (which corresponds to contrast actively extravasating into the hematoma) on postcontrast images strongly predicts hematoma expansion (Figure 71.E3). A scoring system based on the initial size of the hematoma and the number of spots seen is an independent predictor of in-hospital mortality and 3-month outcome.

INTRACRANIAL PRESSURE (ICP) MANAGEMENT

Large intracerebral hemorrhages can cause significant impairment in the level of consciousness. Mass effect from hematoma expansion and intraventricular blood can cause obstruction of cerebrospinal fluid (CSF) flow leading to *acute hydrocephalus*. In these patients, placement of an externalized ventricular drain (EVD) to measure ICP and treat hydrocephalus through CSF diversion is often advocated. If a large amount of intraventricular blood is present, EVDs may become nonfunctional as blood clots within the catheter. A trial is under way to evaluate the safety and efficacy of tPA given through an EVD directly into the ventricle to clear intraventricular blood. This treatment may not only maintain patency of the EVD but also may induce resolution of hydrocephalus and clinical improvement. Temporizing measures such as hyperventilation and hyperosmolar therapies can be utilized until a pathway for CSF diversion is obtained. In some instances, severe mass effect may necessitate surgical decompression through a craniectomy; however, this has not been studied in as much detail as with ischemic stroke.

CORRECTION OF COAGULATION DEFECTS

Patients with primary ICH should have all antiplatelet and antithrombotic agents held, as these can worsen bleeding. Statin medications seem to increase the risk of recurrent ICH due in part to their modest antithrombotic effects, but they may have a beneficial impact on inflammation, so their role in the acute setting is controversial. However, a decision analysis showed that the risk of recurrent ICH with statin use outweighs potential benefits on vascular disease. Other medications (for example, selective serotonin reuptake inhibitors [SSRIs]) can also inhibit platelet function and may be held in the acute setting.

Platelet transfusion to reverse medication effects on platelet function does not seem to be beneficial and is not recommended. On the other hand, if patients present with severe thrombocytopenia, platelets should be given. The desired platelet count in these patients is not clear but greater than 50,000 is probably reasonable. Other systemic conditions (such as renal failure) that cause qualitative platelet dysfunction should be appropriately treated (for example, with desmopressin or hemodialysis [see Chapter 26]).

Coagulopathies that can cause and exacerbate intracerebral bleeding should be aggressively corrected. The most common coagulopathy in patients who present with primary ICH is secondary to anticoagulant medications such as warfarin, heparin, or dabigatran. Supratherapeutic warfarin dosing causes elevations in the international normalized ratio (INR) that can be readily identified on routine coagulation panels. Heparin causes an analogous elevation of the activated partial thromboplastin time (aPTT), although this can be elevated in certain hypercoagulable states as well. In contrast, even though dabigatran can cause a slight elevation in the aPTT, the INR and aPTT are often normal and unreliable indicators of the drug's effect. A direct thrombin time can be measured; however, this option is often not readily available.

Traditionally, warfarin-associated ICH has been treated with a combination of fresh frozen plasma (FFP) and vitamin K; however, FFP first needs to be thawed and subsequent correction can take from several hours up to 1 day. Thus, this strategy is usually too delayed to appropriately limit hematoma expansion. In contrast, prothrombin complex concentrates (PCCs) can rapidly reverse anticoagulant-associated coagulopathies (within 1 hour) and are increasingly being used

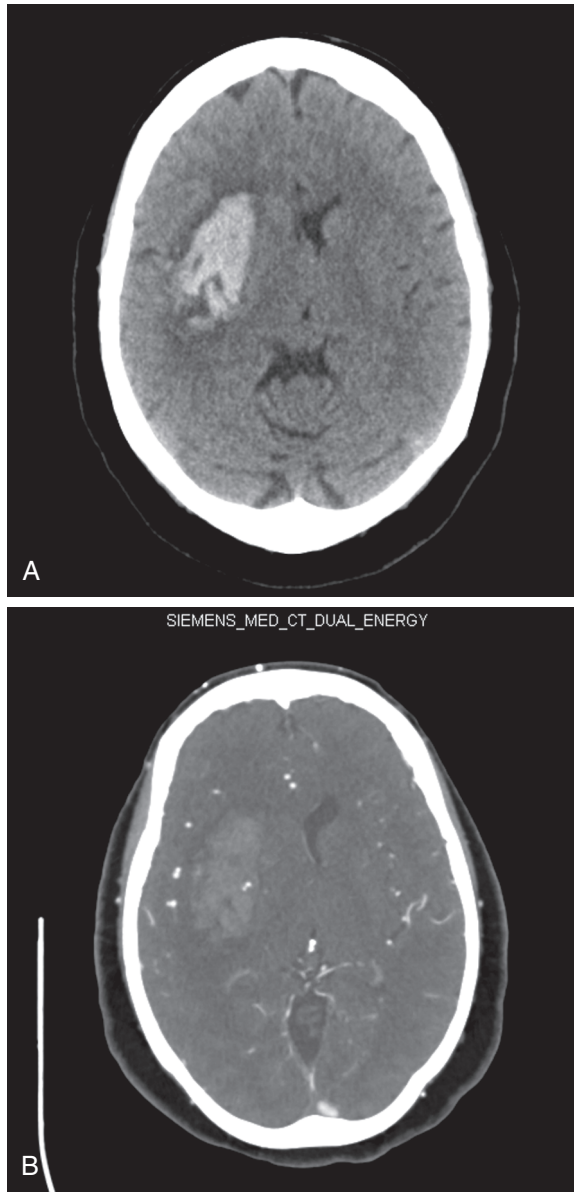


Figure 71.E3 Acute intracerebral hemorrhage. The noncontrast head CT in panel **A** shows an area of subcortical hyperdensity in the right hemisphere corresponding to acute intraparenchymal blood. In panel **B**, a, postcontrast CT angiogram demonstrates hyperdensity within the hematoma cavity (the "spot sign"), which predicts hematoma expansion.

for acute treatment. PCC also requires less volume than FFP and is therefore less likely to induce fluid overload. Effects of unfractionated heparin can be reversed with IV protamine sulfate but not fractionated heparin. The appropriate protocol for reversal of dabigatran-associated hemorrhage is still under debate. PCC has been given as a reversal agent; however, its efficacy is unclear. Hemodialysis may also be considered to remove dabigatran from the circulation and reverse its anticoagulant effects. Optimal strategies for reversal of newer oral systemic anticoagulants such as apixiban and rivaroxaban are not known.

In studies evaluating the efficacy of procoagulants in limiting hematoma expansion in patients without a clear evidence of coagulopathy, the risk of thrombotic complications appears unacceptably high. A phase II randomized controlled trial found that recombinant factor VII limited hematoma expansion; however, a subsequent phase III trial suggested that the increased risk of thrombotic complications in patients receiving factor VII offset the benefit of decreased hematoma size. Further clinical research is required to evaluate whether this is a viable treatment strategy.

BLOOD PRESSURE MANAGEMENT

Aggressive blood pressure management limits hematoma expansion and is advocated in the treatment of ICH. Early arguments suggested that aggressive blood pressure lowering may decrease cerebral blood flow, which could induce ischemia in a vulnerable area surrounding the hematoma (similar to the penumbra seen in ischemic stroke) and cause clinical worsening. However, studies have shown that aggressive blood pressure lowering is safe and does not worsen outcome. Current guidelines suggest lowering blood pressure to < 160/90 mm Hg or a mean arterial pressure (MAP) < 110 mm Hg in patients with blood pressure > 160/90 mm Hg on presentation and normal ICP. In patients who present with blood pressure < 160/90 mm Hg, a more aggressive blood pressure goal such as < 140/80 mm Hg is often used. If there is concern for elevated ICP, a monitor should be placed and blood pressure adjusted so that cerebral perfusion pressure (equal to MAP – ICP) is maintained between 60 to 80 mm Hg. Nicardipine and labetalol are preferred parenteral antihypertensive agents because of their quick onset of action and titratability. Nitroprusside and nitroglycerin should be avoided because they have prominent venodilator activity, which can increase ICP.

MANAGEMENT OF SEIZURES

Perhaps because of the irritative nature of blood products to neural tissue, seizures are common in patients with ICH. If clinical seizures occur, they should be promptly treated, and nonconvulsive seizures should be considered in patients who have decreased levels of consciousness that are out of proportion to what would be expected based on the size and location of the hemorrhage. Continuous electroencephalography (EEG) monitoring is increasingly used to diagnose subclinical seizures. Prophylactic treatment with anti-epileptic medications is not advised, as studies have shown increased mortality when this is done.

An annotated bibliography can be found at www.expertconsult.com.

Management of Subarachnoid Hemorrhage

A detailed description of the management of SAH is beyond the scope of this chapter; however, several general principles can be outlined (see Figure 71.E1). As stated previously, spontaneous SAH most often occurs secondary to a ruptured cerebral aneurysm. Once a diagnosis of SAH is made, management is aimed at preventing rebleeding, vigilant monitoring and treatment of medical and neurologic complications, and prompt surgical or endovascular repair of the rupture.

Recurrence of bleeding after SAH is a major cause of morbidity and mortality, affecting 25% to 40% of patients in the first 3 to 4 days after their initial bleeding event. Two thirds of these recurrent hemorrhages are fatal. Cerebral angiography should be performed as soon as possible to identify the source of bleeding. CT angiography is increasingly being used as an initial imaging modality because of its rapidity and non-invasive nature. Aneurysmal repair can be performed using catheter-based, endovascular techniques (such as stent-assisted coiling) or with traditional open surgery. Aneurysm repair should occur as soon as possible, ideally within the first 72 hours. Prior to repair, blood pressure should be controlled to limit the risk of rebleeding. Overaggressive blood pressure control, however, can cause deleterious hypoperfusion. Current guidelines recommend targeting SBP < 160 mm Hg. If aneurysmal repair cannot be achieved within 72 hours, short-term therapy with parenteral antifibrinolytic agents such as tranexamic acid or aminocaproic acid may be considered.

Seizures are common in SAH, occurring in up to 20% of patients. Short-term prophylactic treatment with antiepileptic drugs is a common clinical practice; however, the impact on outcome is not at all clear and is hotly debated. Treatment with antiepileptic drugs in the immediate post-hemorrhagic period does not seem to alter the risk of developing epilepsy (recurrent seizures) later in life.

One third of all patients with SAH have *acute hydrocephalus*, caused by the obstruction of cerebrospinal fluid (CSF) flow through the ventricular system (Figure 71.E4). These patients typically exhibit drowsiness and, if severe, coma with posturing. The diagnosis can be confirmed by CT and requires prompt intervention with external ventricular drainage. Delayed hydrocephalus, resulting from blockage in absorption of CSF, occurs in a small fraction of patients and may require permanent ventricular shunting.

Vasospasm is another complication of SAH, generally occurring between the 4th and 10th day after the initial event. Vasospasm may be a misnomer for a syndrome of delayed cerebral ischemia after SAH that has a complex pathophysiology. Focal neurologic symptoms or confusion are manifestations of vasospasm, which, if persistent, may result in infarction. The calcium channel blocker nimodipine should be administered daily, as it has been shown to benefit mortality. Transcranial Doppler studies may be helpful in screening for areas of vasospasm.

Finally, multiple medical complications including cardiac dysfunction (often from a catecholamine surge causing myocardial contraction band necrosis and a stress [Takotsubo's] cardiomyopathy [Chapter 50]) and hyponatremia (either from syndrome of inappropriate antidiuretic hormone (SIADH) or cerebral salt wasting [see Chapter 84]) are commonly seen. Vigilance and frequent monitoring are required to promptly identify these complications and treat them appropriately.

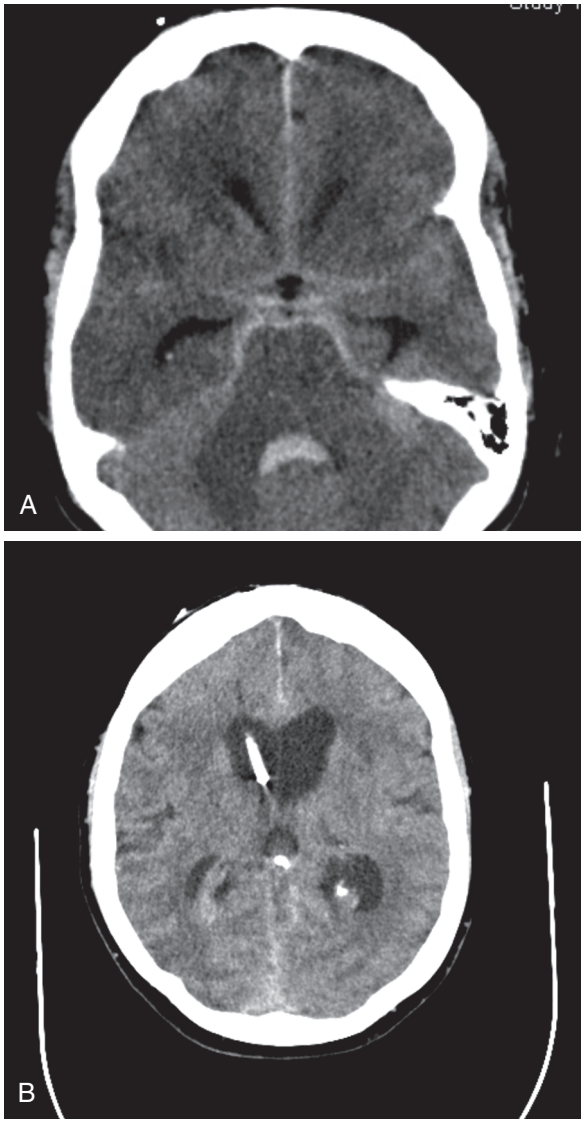


Figure 71.E4 **A** and **B,** aneurysmal subarachnoid hemorrhage causing acute hydrocephalus. There is hyperdense material seen in the proximal sylvian fissures bilaterally, within the prepontine cistern (causing the brain stem to be outlined by blood) and within the fourth ventricle. The fourth ventricular blood has caused hydrocephalus, as shown by dilation of the third and lateral ventricles in panel **B**. A ventriculostomy catheter can be seen terminating in the right lateral ventricle.

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CHAPTER 72

Obstetric and Postobstetric Complications

Lisa D. Levine ■ Samuel Parry

Chapter 28 describes maternal physiologic adaptations to pregnancy and provides guidelines for the care of pregnant patients who are admitted to the intensive care unit (ICU) for *nonobstetric* indications. This chapter discusses the management of pregnant patients admitted to the ICU for *obstetric indications,* including obstetric hemorrhage, preeclampsia or eclampsia, acute fatty liver of pregnancy (AFLP), amniotic fluid embolism, and severe pulmonary edema.

Obstetric Hemorrhage

ANTEPARTUM HEMORRHAGE

In any pregnant patient who presents with third-trimester vaginal bleeding, ultrasonography should be performed before pelvic examination to exclude the diagnosis of placenta previa and to detect a fetal heart rate.

Differential Diagnosis

There are multiple causes of antepartum hemorrhage (Table 72.1). Abruptio placenta (separation of the placenta from the uterine wall) and placenta previa (placenta implanted over the uterine cervix) may be associated with substantial maternal blood loss in part because of the inability of fibrinized spiral uterine arteries to vasoconstrict. The dissection of blood between the fetal membranes and the maternal decidua often initiates uterine contractions. These contractions may exacerbate the bleeding and precipitate repeated bleeding episodes.

Fetal anemia may be associated with bleeding from placental villous vessels. Primary fetal bleeding is associated with a velamentous cord insertion in which the umbilical cord inserts at a distance from the placenta such that fetal vessels must traverse the placental membranes. A vasa previa occurs when unprotected fetal vessels traverse the uterine cervix. Velamentous cord insertion and vasa previa are rare causes of third-trimester vaginal bleeding.

Laboratory Evaluation

Laboratory evaluation includes a complete blood count (CBC), prothrombin time and partial thromboplastin time, fibrinogen and fibrin degradation (split) product levels, including D-dimer, and a Kleihauer-Betke (KB) stain. A KB stain is an acid elution test that is used to detect fetal hemoglobin in the maternal blood and to calculate the volume of fetomaternal hemorrhage. In an unsensitized Rh-negative mother with antepartum bleeding, Rho immune globulin (RhoGAM) should be given to prevent maternal production of anti-D antibodies. A standard vial (300 mg) of Rho immune globulin provides prophylaxis for a 30-mL fetomaternal hemorrhage. Larger fetomaternal hemorrhages, as calculated by KB stain, require additional Rho immune globulin (10 mg/mL fetal whole blood). If the fetomaternal hemorrhage

TABLE 72.1 ■ **Selected Causes of Third-Trimester Vaginal Bleeding**

Cause	Risk Factors	Comments
Abruptio placenta	Hypertension	Usually associated with abdominal tenderness and uterine contractions
	Cocaine use	
	Trauma	20% of cases have concealed hemorrhage (no vaginal bleeding)
		Rarely visualized by ultrasonography
Placenta previa	Prior cesarean section	Usually no abdominal tenderness, but uterine contractions are common
		Ultrasonography confirms diagnosis
Uterine rupture	Prior (classic [i.e., via vertical uterine incision]) cesarean section	Acute, persistent, intense abdominal pain
Fetal bleeding	Velamentous umbilical cord insertion	Smear of vaginal bleeding demonstrates nucleated red blood cells (i.e., cells of fetal origin)
	Vasa previa	Apt alkali test shows differential resistance of fetal and maternal oxyhemoglobin to sodium hydroxide
		Ultrasonography to evaluate umbilical cord location

BOX 72.1 ■ Obstetric Conditions Associated with Disseminated Intravascular Coagulation

Preeclampsia, HELLP syndrome, AFLP
Amniotic fluid embolism
Fetal death syndrome
Gestational trophoblastic neoplasia
Obstetric hemorrhage
Septic abortion

AFLP, acute fatty liver of pregnancy; HELLP, hemolysis, elevated liver enzymes, and low platelets.

is calculated to exceed 50 mL, the risk for severe fetal anemia is great, and early delivery must be considered.

Maternal coagulation studies are of critical importance in patients with obstetric hemorrhage because of the risk of disseminated intravascular coagulation (DIC) (Box 72.1). In these patients, the coagulation cascade is activated by the release of large amounts of tissue phospholipids, endotoxin, or both, which produce maternal endothelial damage. Obstetric patients diagnosed with DIC should be aggressively supported with transfusions of plasma or cryoprecipitate and platelets. However, DIC resolves only when the underlying cause of DIC is resolved.

Management

A patient with antepartum obstetric hemorrhage requires continuous fetal heart rate monitoring. "Nonreassuring" fetal heart rate patterns may necessitate emergency delivery. Large-bore intravenous (IV) access should be established, and aggressive volume replacement with crystalloids, blood components, or both should be initiated. In the setting of antepartum obstetric hemorrhage, tocolysis may be considered if the mother and fetus are stable and there is evidence for preterm labor in association with cervical dilatation. Because beta-sympathomimetic tocolytics

(terbutaline, ritodrine) produce maternal tachycardia and peripheral vasodilatation, both may mimic signs of continued bleeding. Thus, magnesium sulfate is probably the tocolytic agent of choice. Delivery options are decided based on maternal and fetal clinical conditions, gestational age, and fetal lung maturity.

POSTPARTUM HEMORRHAGE

Postpartum hemorrhage may be broadly classified into uterine or nonuterine bleeding. Uterine bleeding, responsible for 90% of cases of postpartum hemorrhage, is generally more severe than nonuterine causes. Because the uterus receives 20% of the maternal cardiac output at term (about 600 mL/min), rapid control of postpartum uterine bleeding is critical.

Clinical History and Risk Factors

Uterine atony is defined as the failure of prompt myometrial contraction after the third stage of labor. It is associated with multiparity, uterine overdistention (multifetal gestation), protracted labor, and infection. Unfortunately, uterine atony is often idiopathic and cannot be anticipated. *Retained placenta* is frequently associated with uterine atony and difficult delivery of the placenta. Retained placenta usually presents as delayed (> 24 hours) postpartum hemorrhage often in association with endomyometritis. *Placenta accreta*, a type of abnormal placentation in which the placenta invades through the maternal decidua and attaches directly to the myometrium, is strongly associated with prior cesarean section and placenta previa. This abnormal attachment makes removing the placenta from the uterus difficult and often requires a cesarean hysterectomy and massive transfusion. *Uterine rupture* occurs most frequently with vaginal delivery after a previous cesarean section, although the risk for scar dehiscence is less than 1% if the previous incision was confined to the lower uterine segment. Under these conditions, the overall maternal morbidity for a trial of labor has been demonstrated to be less than that of repeat cesarean section.

Nonuterine causes of postpartum hemorrhage include lower genital tract lacerations, which should be suspected after a difficult operative vaginal delivery, hematomas (which may be subclassified as vulvar or pelvic), and coagulopathies. Vulvar hematomas often present as early perineal pain, whereas pelvic hematomas (defined as occurring above the levator ani muscles) usually occur after cesarean delivery.

Physical Examination and Laboratory Findings

The physical examination and laboratory findings typically allow the physician to identify the cause of postpartum hemorrhage rapidly. Physical examination must include an abdominal and pelvic examination, with visualization of the entire vagina and cervix and palpation of the uterine cavity. Pelvic ultrasonography and a CBC and coagulation profile may assist in diagnostic and therapeutic decisions. The diagnosis of *uterine atony* is confirmed when brisk vaginal bleeding is encountered after delivery in association with a boggy, flaccid uterus. *Retained placenta* presents similarly (although often many hours later), and ultrasonography may be used to visualize retained products of conception within the uterine cavity. Because the retained placenta is a nidus for infection, the patient may have an elevated temperature and a tender uterine fundus. *Placenta accreta* is readily identified by manual exploration of the uterine cavity and finding placenta remaining adherent to the uterine wall. Pelvic examination including manual exploration of the uterine cavity and visualization of the entire lower genital tract allows the physician to identify *uterine scar dehiscence, lower genital tract lacerations,* and *vulvar hematomas* readily. *Pelvic hematomas* may be concealed but can generally be visualized by ultrasonography when suspected in a postpartum patient with a decreasing hemoglobin and hematocrit.

BOX 72.2 ■ Management of Postpartum Hemorrhage

Nonsurgical Approaches

- Bimanual uterine compression (facilitated by an empty bladder)
- Intravenous oxytocin (20 units in 1000 mL of crystalloid at a brisk infusion rate)
- Intramuscular or intramyometrial 15-methyl prostaglandin $F_{2\alpha}$ (0.25 mg), repeat every 10 to 15 minutes
- Intramuscular methylergonovine (Methergine) 0.2 mg (may produce transient but extreme blood pressure elevations and is contraindicated in hypertensive patients)
- Uterine packing performed only after confirming the absence of lower genital tract laceration, uterine rupture, and uterine inversion; a Bakri balloon is placed in the lower uterine segment and inflated with 500 cc of sterile saline and kept in place for 24 to 36 hours; alternatively, the entire uterus and vagina may be packed; prophylactic antibiotics and continuous oxytocin are recommended
- Angiographic embolization of bleeding vessels

Surgical Approaches

- Postpartum dilation and curettage (for retained placenta)
- Surgical ligation of pelvic vessels (uterine and hypogastric arteries) to decrease arterial pulse pressures (vessels later recanalize and have no effect on subsequent fertility)
- Postpartum hysterectomy

Management

Although postpartum hemorrhage is generally managed medically, if medical techniques fail or a laceration is identified, surgical procedures are indicated (Box 72.2). Central hemodynamic monitoring is indicated if massive volume replacement is needed. Because physiologic intravascular mobilization of extracellular fluid occurs after delivery, fluid replacement therapy places such a patient at increased risk for pulmonary edema.

Postpartum Preeclampsia

The cause of preeclampsia is yet to be elucidated, but the disease appears to be related to abnormal placentation. This leads to the release of unknown endogenous factors, resulting in generalized maternal vasospasm and endothelial cell damage. Diminished blood flow to the uterus and maternal end organs precipitates the various complications associated with severe preeclampsia. Although the cure for preeclampsia is delivery of the fetus and placenta, residual disease frequently persists and may even progress for more than 24 to 48 hours into the postpartum period.

CLINICAL DIAGNOSIS

The diagnosis of preeclampsia is based simply on the presence of sustained maternal hypertension (defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) in the second half of pregnancy in a previously normotensive woman in association with proteinuria. Postpartum complications considered to be due to preeclampsia are listed in Box 72.3.

LABORATORY ABNORMALITIES

Abnormal laboratory test results reflect the clinical manifestations of diminished blood flow to end organs and endothelial cell damage. Because of the increased glomerular filtration rate and increased renal plasma flow in pregnancy, a normal serum creatinine level is considered to be ≤ 0.6 mg/dL. However, in women with preeclampsia, decreased renal plasma flow and glomerular

BOX 72.3 ■ Postpartum Complications Associated with Severe Preeclampsia

Central nervous system manifestations other than seizures (subarachnoid hemorrhage and cerebral infarct)
Disseminated intravascular coagulation (DIC)
Eclampsia (generalized seizures)
HELLP syndrome
Hepatic infarct and rupture
Oliguria and acute renal failure
Pulmonary edema
Refractory hypertension

HELLP, hemolysis, elevated liver enzymes, low platelets.

capillary endothelial damage result in decreased creatinine clearance, increased serum creatinine levels, increased blood urea nitrogen levels, and oliguria (< 50 mL/h). As previously noted, a serum creatinine level of > 0.6 mg/dL is considered elevated, and once the creatinine has reached 1 mg/dL, impairment in more than 50% of the renal function has occurred. Intravascular volume depletion secondary to generalized vasospasm causes hemoconcentration. Endothelial cell damage stimulates the coagulation cascade with consumption of platelets and coagulation factors, most frequently manifesting with a decrease in serum fibrinogen levels. Hepatocellular necrosis due to decreased hepatic perfusion results in elevated bilirubin and liver enzyme levels.

The HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome complicates 10% to 20% of pregnancies with severe preeclampsia. HELLP syndrome was originally defined as including all these factors, but any one of them may represent severe disease. The criteria for the HELLP syndrome include (1) evidence of hemolysis by the presence of schistocytes on blood smear (see Figure 45.1 in Chapter 45), an elevated indirect bilirubin level, or lactate dehydrogenase levels > 600 IU/L; (2) a total bilirubin level ≥ 1.2 mg/dL; (3) aspartate aminotransferase (AST) levels > 70 IU/L (or twice the upper limit of normal); and (4) platelet counts < 100,000/μL. Maternal morbidity and mortality correlate with the fall in platelet counts. Those with platelet counts < 50,000/μL are the most severely affected and may benefit from dexamethasone treatment.

Patients with HELLP syndrome often present with malaise, nausea, headache, and right upper quadrant pain. HELLP syndrome must be differentiated from other conditions causing liver disease in pregnancy (Table 72.2). The differential diagnosis of hemolysis and thrombocytopenia includes (1) thrombotic thrombocytopenic purpura (TTP), which presents with a more severe microangiopathic hemolytic anemia, central nervous system abnormalities, renal manifestations, and fever (see Chapter 63); (2) hemolytic uremic syndrome (HUS), which has more severe renal failure; and (3) idiopathic thrombocytopenic purpura (ITP), which is not associated with hypertension, elevated liver enzyme levels, or proteinuria (see Chapter 63).

MANAGEMENT

Therapy of postpartum preeclampsia has three basic goals: seizure prophylaxis, control of hypertension, and supportive therapy for its various complications. Magnesium sulfate has been shown to be the most effective drug for prevention and treatment of eclamptic seizures. Standard administration of magnesium sulfate is a 4- to 6-g IV loading dose in 50 to 100 mL of 0.9% (normal) saline over 20 minutes, followed by a maintenance dose of 2 g/h for 24 hours after delivery. The therapeutic range of plasma magnesium for preventing eclamptic seizures is 4 to 7 mEq/L. Plasma magnesium levels should be monitored closely, particularly in patients who have renal dysfunction. An initial magnesium level should be measured 1 hour after the loading dose is

TABLE 72.2 ■ **Differential Diagnosis of Liver Disease in Pregnancy**

Condition	Aspartate Aminotransferase Levels (IU/L)	Total Bilirubin (mg/dL)	Liver Histologic Features	Other Features
AFLP	< 500	< 5	Fatty infiltration	Hypoglycemia Renal failure
Acute hepatitis B	1000–2000	> 5	Hepatocellular necrosis	Perinatal transmission
HELLP syndrome	> 500	< 5	Hepatocellular necrosis	Hypertension Thrombocytopenia Hemolysis with schistocytes
Intrahepatic cholestasis	< 300	< 5 (mostly direct)	Dilatated bile canaliculi	Pruritus

AFLP, acute fatty liver of pregnancy; HELLP, hemolysis, elevated liver enzymes, low platelets.

completed. Clinical evaluation must include frequent monitoring of mental status, deep tendon reflexes, respiratory effort, and urine output. Patellar reflexes usually are lost at levels of 8 to 10 mEq/L, and respiratory arrest may occur at 13 mEq/L. Calcium gluconate (1 g, available as 10 mL of 10% solution) must be readily accessible for IV administration to reverse symptomatic magnesium toxicity (e.g., obtundation, apnea).

Antihypertensive agents are typically administered when blood pressure exceeds 160 mm Hg systolic or 110 mm Hg diastolic. Hydralazine has been widely used as a 5- to 10-mg IV bolus, which may be repeated every 20 minutes as necessary. Alternatively, labetalol may be given as a 10 mg IV bolus, with increasing boluses (20 mg, 40 mg, 80 mg) repeated every 10 minutes to a total dose of 300 mg. After desired blood pressures are attained, an IV labetalol drip may be instituted at 1 to 2 mg/min and then titrated. Occasionally, refractory high blood pressure may require the administration of potent vasodilators, such as sodium nitroprusside (Chapter 53), usually with central hemodynamic monitoring.

Several disorders other than refractory hypertension are indications for central hemodynamic monitoring in the postpartum preeclamptic patient: general anesthesia in an unstable patient, pulmonary edema, and oliguria. Because central venous pressure correlates poorly with pulmonary artery wedge pressure in preeclamptic patients, use of a pulmonary artery catheter is preferred.

Acute Fatty Liver of Pregnancy

The incidence of AFLP is rare (1 in 10,000 to 100,000 pregnancies). Its cause is unknown. Although ~50% of AFLP cases are associated with preeclampsia, these two disease processes have distinct patterns of liver pathology. The histologic and clinical features that differentiate AFLP from other liver diseases in pregnancy are outlined in Table 72.2.

CLINICAL MANIFESTATIONS

The clinical manifestations of AFLP include generalized malaise and central nervous system complaints ranging from headache to obtundation and coma. Patients often report nausea and vomiting, right upper quadrant pain, and gastrointestinal bleeding. Examination may reveal jaundice and right upper quadrant tenderness but no hepatomegaly.

LABORATORY ABNORMALITIES

Laboratory tests may reveal moderately elevated liver function test results, hypoglycemia (secondary to impaired glycogen synthesis), and a consumptive coagulopathy caused by consumption of clotting factors (which is worsened by decreased hepatic synthesis). Patients may experience hepatorenal failure with oliguria and increased blood urea nitrogen and creatinine levels. Metabolic acidosis may be seen if multiple organ system failure develops.

TREATMENT

Therapy is supportive, with an emphasis on correcting metabolic derangements, maintaining oxygenation, and restoring renal and mental function. Intravenous fluid therapy with glucose-containing solutions should maintain serum glucose at > 60 mg/dL. Restricting protein intake and giving lactulose by mouth or nasogastric tube aim to prevent elevations of plasma ammonia. Stress ulcer prophylaxis should be initiated to reduce the risk of gastrointestinal hemorrhage. Coagulation abnormalities may be improved by administering clotting factors, and renal failure may require temporary hemodialysis. These patients are at high risk for nosocomial infection.

Several management options have been attempted to treat patients who are deteriorating despite traditional supportive measures. These strategies include plasmapheresis and liver transplantation (Chapter 59). Before 1980, the reported survival rate for AFLP was only 25%; since then, however, improved ICU supportive care has increased survival rates to more than 90%.

Amniotic Fluid Embolism

Amniotic fluid embolism occurs in 1 in 30,000 pregnancies, most commonly during labor. Occasionally it happens early (e.g., during a first-trimester dilation and curettage) or late (e.g., 48 hours postpartum). Amniotic fluid embolism has been associated with protracted labor. A release of amniotic fluid into the maternal (pulmonary) vasculature appears to be its cause, but it is not clear whether the volume of infusate or the presence of biologically active substances in the amniotic fluid is more important. Fetal squamous cells have been detected in the pulmonary vasculature of pregnant mothers who had a pulmonary artery catheter for reasons other than amniotic fluid embolism. This indicates that amniotic fluid in the maternal pulmonary vasculature is not pathognomonic for amniotic fluid embolism. It also suggests that noxious substances in the amniotic fluid (i.e., arachidonic acid metabolites) may primarily be responsible for the endothelial cell damage and cardiopulmonary changes associated with amniotic fluid embolism syndrome.

CLINICAL PRESENTATION

Patients with amniotic fluid embolism most commonly present with acute respiratory distress, cyanosis, and cardiovascular collapse. The patient usually has mental status changes that ultimately may lead to coma. Clinical bleeding associated with DIC is seen in 40% to 50% of patients. The cause of DIC is unknown, but trophoblasts are known to have thromboplastin-like effects.

Acute pulmonary hypertension is transient (< 1 hour) and often resolves before hemodynamic monitoring and ICU admission. A hemodynamic picture consistent with left ventricular failure (elevated pulmonary artery wedge pressure and low cardiac output) is commonly encountered. Left ventricular failure may result from myocardial hypoxia (caused by decreased coronary artery flow) or direct myocardial injury from noxious substances. Pulmonary capillary endothelial injury may also result in the acute respiratory distress syndrome (ARDS).

Treatment

Therapy is supportive and includes maintenance of oxygenation, cardiac output, and blood pressure. The coagulopathy may not resolve quickly, and clotting factors may be replaced to maintain adequate clotting function until the patient improves clinically.

Pulmonary Edema

Pulmonary edema may be a result of preeclampsia or, rarely, a result from tocolysis. Pulmonary edema complicates 3% to 5% of cases of severe preeclampsia, with 70% occurring postpartum. Beta-sympathomimetic agents are widely used for tocolysis in the management of preterm labor. Ritodrine (no longer marketed in the United States) and terbutaline are relatively $beta_2$-selective agents that diminish the frequency of extreme maternal sinus tachycardia. When these agents are appropriately administered with free water and accurate monitoring of the patient's fluid intake and output, the incidence of tocolysis-induced pulmonary edema is < 1%.

ETIOLOGY

Pulmonary edema associated with preeclampsia is multifactorial and results from a decrease in oncotic pressure, fluid overload, increased capillary permeability, and an increase in pulmonary capillary hydrostatic pressure. Pulmonary edema from preeclampsia may present as flash pulmonary edema or may develop more insidiously during labor. The mechanism of tocolysis-induced pulmonary edema has not been completely elucidated. Several mechanisms have been proposed based on the known pharmacologic effects of parenteral beta-sympathomimetics. Their renal effects result in sodium and water retention secondary to enhanced distal tubular sodium reabsorption and increased secretion of vasopressin, respectively. Sodium and water retention, in conjunction with the large amounts of IV fluids often administered to these patients, increases the intravascular hydrostatic pressure, driving fluid into the pulmonary interstitium. Additionally, endothelial damage secondary to toxins released by subclinical intrauterine infection (often associated with preterm labor) may cause increased permeability of pulmonary capillaries. These factors contribute to a clinical picture of pulmonary edema resulting from a combination of volume overload and increased permeability.

CLINICAL PRESENTATION

Both preeclampsia-associated pulmonary edema and beta-agonist-tocolysis–induced pulmonary edema often present with rapidly progressive shortness of breath with chest discomfort and tachypnea. Physical examination reveals hypoxia and bilateral rales, and it may precede a chest radiograph demonstrating pulmonary edema. Arterial blood gas analysis typically shows hypoxemia. The possibility of concurrent infection (chorioamnionitis, urinary or respiratory tract) must be carefully investigated.

MANAGEMENT

Therapy for preeclampsia-associated pulmonary edema includes diuresis with furosemide. Preeclampsia is associated with intravascular volume depletion and therefore central venous monitoring should be initiated when diuretic therapy is given to women with preeclampsia-associated pulmonary edema and oliguria to assure maintenance of a euvolemic state. Therapy for beta-agonist-tocolysis–induced pulmonary edema includes oxygen, morphine, or fentanyl administration to relieve dyspnea and decrease venous return; aggressive diuresis with furosemide; and discontinuation of the beta-agonist tocolytic agent. Other tocolytic agents, such as magnesium

sulfate or indomethacin, may be considered if intrauterine infection is not present. Caution must be exercised when administering magnesium sulfate, because it can cause respiratory depression at toxic levels, and indomethacin, because it can diminish renal function. The maximal IV fluid volume should not exceed 2500 mL/day. Central hemodynamic monitoring is seldom required for tocolysis-induced pulmonary edema. However, if the patient fails to improve after diuresis, such monitoring may be needed, and other diagnoses, including pulmonary embolism and peripartum cardiomyopathy, must be considered.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 73

Acute Lung Injury and Acute Respiratory Distress Syndrome

John P. Reilly ■ Paul N. Lanken

The acute respiratory distress syndrome (ARDS) is common in the intensive care unit (ICU) setting, with an estimated 190,000 cases per year in the United States and a high mortality, generally between 20% and 40%. ARDS is the term used to describe a syndrome of acute noncardiogenic pulmonary edema that occurs after various systemic or local insults. It is a respiratory disorder that meets four general clinical criteria: (1) acute onset, (2) poor oxygenation, (3) bilateral chest radiographic infiltrates, and (4) conditions that are unexplained by cardiac failure or fluid overload.

Since 1994, both acute lung injury (ALI) and ARDS were defined by criteria of the American European Consensus Conference (AECC) (Table 73.1A) with ARDS defined as a more severe subset of ALI. However, in 2012, a panel of experts meeting in Berlin published the "Berlin definition" to address ambiguities of the prior AECC criteria and to improve the accuracy and usefulness by applying various criteria stepwise to existing databases of patients with ALI and ARDS (Table 73.1B). According the Berlin definition, ARDS encompasses the same Pao_2/Fio_2 range of the old ALI, which would now be an obsolete term. The new definition of ARDS also details mild, moderate, and severe forms of the syndrome based on the Pao_2/Fio_2 ratio. Patients who previously were diagnosed with ALI but not ARDS ($Pao_2/Fio_2 \leq 300$, but > 200) are now referred to as patients with mild ARDS. Because this modification to the definition of ARDS was published in 2012, virtually all of the literature published from 1994 to 2012 has utilized the AECC definition of ALI and ARDS.

Synonyms for ARDS include noncardiogenic pulmonary edema, shock lung, permeability pulmonary edema, and pulmonary capillary leak syndrome. The latter two terms arise from the concept that pulmonary edema in patients with ARDS is due primarily to increased permeability of the alveolar-capillary membrane at normal or modestly elevated pulmonary capillary pressures. In contrast, pulmonary edema in left-sided congestive heart failure (CHF) (i.e., elevated left atrial pressure) results from excessive filtration of plasma across the alveolar-capillary membrane as a result of the hydrostatic forces created by high pulmonary capillary pressure (see Chapter 52).

Pathogenesis and Precipitating Causes

ARDS results from injury to the alveolar-capillary membrane that is caused by exogenous agents or by endogenous inflammatory mediators. This injury results in leakage of plasma into the lung's interstitial and alveolar spaces, with the end result being alveolar flooding and respiratory failure. It is a *final common pathway* in response to various initial systemic insults, including sepsis, pneumonia, and severe trauma (Box 73.1). For most of these predisposing conditions, only a minority

TABLE 73-1A ■ **A Recommended Criteria for Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)**

	Timing	Oxygenation	Chest Radiograph	Pulmonary Artery Wedge Pressure
ALI criteria	Acute onset	$Pa_{O_2} \leq 300$ mm Hg (regardless of PEEP level)	Bilateral infiltrates seen on frontal chest radiograph	≤ 18 mm Hg when measured or no clinical evidence of left atrial hypertension
ARDS criteria	Acute onset	$Pa_{O2}/F_{IO_2} \leq 200$ mm Hg (regardless of PEEP level)	Bilateral infiltrates seen on frontal chest radiograph	≤ 18 mm Hg when measured or no clinical evidence of left atrial hypertension

Modified from Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS. Am J Respir Crit Care Med 149:818–824, 1994.

TABLE 73.1B ■ **Criteria for the Acute Respiratory Distress Syndrome (ARDS) published by the The ARDS Definition Task Force (AKA "The Berlin Definition")**

Criteria	Acute Respiratory Distress Syndrome (ARDS)
Acute onset	Within 1 week of known clinical insult or new or worsening respiratory symptoms
Radiographic studies	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Etiology of edema	Respiratory failure not fully explained by cardiac failure or fluid overload
Hypoxemia	Mild ARDS: $200 < Pa_{O_2}/F_{IO_2} \leq 300$ with PEEP or CPAP ≥ 5 cm H_2O
	Moderate ARDS: $100 < Pa_{O_2}/F_{IO_2} \leq 200$ with PEEP ≥ 5 cm H_2O
	Severe ARDS: $Pa_{O_2}/F_{IO_2} \leq 100$ with PEEP ≥ 5 H_2O

Modified from The ARDS Definition Task Force: Acute Respiratory Distress Syndrome: The Berlin Definition. JAMA 307:2526-2533, 2012.

Pa_{O_2}, arterial partial pressure of oxygen; F_{IO_2}, fraction of inspired oxygen; PEEP, positive end expiratory pressure; CPAP, continuous positive airway pressure.

BOX 73.1 ■ Common Causes of the Acute Respiratory Distress Syndrome

Direct Causes of Lung Injury

- Aspiration pneumonia
- Pneumonias (viral, bacterial, pneumocystis, atypical pneumonias, *Legionella*) (see Chapter 65)
- Smoke and toxic gas inhalation (see Chapter 56)
- Trauma to thorax with lung contusion (see Chapter 100)
- Primary graft dysfunction after lung transplantation
- Near drowning

Indirect Causes of Lung Injury

- Acute pancreatitis (see Chapter 58)
- Fulminant hepatic failure (see Chapter 59)
- Massive blood transfusion with transfusion-related lung injury (TRALI; see Chapter 46)
- Severe trauma without lung contusion, but especially with multiple fractures with fat emboli syndrome
- Postcardiopulmonary bypass (see Chapter 88)
- Severe sepsis and septic shock (see Chapter 10)

of patients at risk actually go on to have full-blown ARDS. Although it is unclear why ARDS develops in some at-risk patients and not others, the risk of ARDS increases several-fold if the patient has multiple predisposing conditions. To date, no pharmacologic intervention has been effective in preventing ARDS in at-risk patients.

Clinical Considerations

CLINICAL FEATURES

Patients with ARDS typically present with acute respiratory distress at the same time as, or shortly after, one or more of the associated precipitating causes (see Box 73.1). Their physical examination is notable for signs of respiratory distress, rapid shallow respirations with or without scattered inspiratory crackles. They often have orthopnea but no other signs of CHF. Chest radiographs often show characteristic diffuse bilateral infiltrates without cardiac enlargement. Initially, the infiltrates may be interstitial and then progress to widespread and confluent alveolar densities.

Arterial blood gas (ABG) results in very early ARDS are notable for hypoxemia, but often, there is *hypocapnia* with a primary respiratory alkalosis. Pao_2 typically remains low, despite supplemental oxygen, because of the pulmonary shunt created by flooded alveoli (see Chapter 1). A high respiratory rate and an increased work of breathing rapidly lead to respiratory muscle fatigue, *hypercapnia*, and need for intubation and mechanical ventilation. Because many patients with ARDS have associated life-threatening conditions, such as hemorrhagic or septic shock, their ARDS may become evident only after initial stabilization and volume resuscitation.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is relatively short and includes cardiogenic pulmonary edema and a few acute conditions with large right-to-left shunts that cause severe hypoxemia. Examples of the latter include severe atelectasis (especially if hypoxic pulmonary vasoconstriction is blunted by vasodilators), opening of a patent foramen ovale as a result of acute pulmonary hypertension arising from a major acute pulmonary embolus, acute eosinophilic pneumonia, and diffuse alveolar hemorrhage.

Unlike AECC definitions of ARDS, the current Berlin definition does allow for concomitant ARDS and cardiogenic pulmonary edema. However, it is still important to differentiate ARDS from pulmonary edema resulting primarily from cardiac failure or fluid overload. Evidence in favor of CHF includes a cardiac history, an enlarged heart on chest radiograph, and a third heart sound. Rapid improvement after diuresis strongly suggests CHF without concomitant ARDS. If a pulmonary artery (PA) catheter is present, a pulmonary artery wedge pressure (PAWP) of ≤ 18 mm Hg supports the diagnosis of ARDS. However, PAWPs of 19 to 22 mm Hg are not uncommon after fluid resuscitation in patients previously diagnosed on clinical grounds prior to insertion of the PA catheter. Conversely, PAWPs in the 19 to 22 mm Hg range or even ≤ 18 mm Hg may be present at the time of measurement in some patients with CHF. One example of the latter is the patient who undergoes diuresis in the interval between the occurrence of pulmonary edema and PAWP determination. Another example is the patient who has "flash pulmonary edema," in which transient ischemia-induced left ventricular dysfunction or papillary muscle dysfunction resolves before PAWP measurement. In general, cardiogenic pulmonary edema to the degree of confluent alveolar flooding and respiratory failure is associated with PAWP > ~28 to 30 mm Hg in patients with normal oncotic pressure and is primarily due to the imbalance of their Starling forces across the alveolar-capillary membrane.

Mechanisms of Lung Injury

ACUTE EXUDATIVE PHASE IN EARLY ARDS

ARDS has been recognized to progress through several pathologically distinct phases characterized by different clinical and pathologic characteristics. Early-phase ARDS, known as the exudative phase, presents as failure of the lungs alone (single-organ failure) or as failure of the lungs with failure of other organs at the same time as part of the syndrome of multiorgan system failure (MOSF). At the beginning of this phase, no morphologic changes may be seen histologically or ultrastructurally other than interstitial edema resulting from alveolar capillary barrier dysfunction. After gross alveolar edema forms, a pattern of diffuse alveolar damage (DAD) is present. On histologic examination, protein-rich edema with various inflammatory cells fills the alveoli. Hyaline membranes, made up of fibrin strands, form a pseudoepithelium over denuded alveolar basement membranes. The edema may be severe, with lungs from patients with ARDS each weighing more than 1000 g each, a figure that is several times normal.

Overdistention of alveoli resulting from large tidal volumes ("volutrauma" or ventilator-induced lung injury [VILI]) produced by positive pressure mechanical ventilation and positive end-expiratory pressure (PEEP) also contributes to the acute exudative phase by augmenting the original injury. Evidence from animal and in vitro lung experiments indicates that subjecting normal lungs to large tidal volume ventilation (by positive or negative distending pressures) results in the production and release of proinflammatory cytokines and the histologic appearance of DAD. In addition, ventilation of lungs of experimental animals at physiologically appropriate-sized tidal volumes but without any end-expiratory distending pressure, PEEP, can cause release of the same cytokines and lung injury (referred to as a repetitive opening and closing lung injury). Systemic release of these proinflammatory mediators from the lung has been associated with cellular injuries to remote organs and subsequent development of MOSF. These mechanistic findings form the basis underlying the strategy of low tidal volume mechanical ventilation, which is the only ventilation approach that has significantly improved survival in patients with ARDS.

FIBROPROLIFERATIVE PATTERN IN LATE-PHASE ARDS

In patients with ARDS who survive the acute exudative phase, alveolar and interstitial remodeling begins after the lung injury is widespread and well established. This may be as early as 1 week after onset and is termed the fibroproliferative phase of ARDS. Type II pneumocytes proliferate after loss of the type I cells and eventually differentiate into new type I pneumocytes to reconstitute the alveolar epithelium. In response to mediators released by the inflammatory process in ARDS with possible contributions from oxygen toxicity, fibroblasts proliferate, migrate, and produce collagen, resulting in alveolar and interstitial fibrosis.

Oxygen toxicity may contribute to the pathologic changes in most cases of late-phase ARDS, but its exact role remains uncertain. Patients with ARDS are virtually always exposed to a high oxygen concentration, which is by itself a cause of acute lung injury in animal models. The level of F_{IO_2} that is nontoxic for patients with injured lungs remains unknown. These fibroproliferative changes may be marked in some patients and may cause death either from progressive hypoxemic respiratory failure or from nosocomial pneumonia and sepsis.

Pathophysiology of ARDS

HYPOXEMIA

In early-phase ARDS, the most life-threatening problem is severe hypoxemia. This arises predominantly from a large right-to-left intrapulmonary shunt through numerous fluid-filled alveoli

(see Chapter 1). Its magnitude can be estimated as follows: a 5% shunt is present for every 100 mm Hg decrease in Pao_2 below 700 mm Hg while the patient is breathing 100% oxygen. For example, if Pao_2 on 100% oxygen is 200 mm Hg, then the shunt is ~25%. (This estimate is accurate only for Pao_2 values above 150 mm Hg.) Patients with ARDS who need mechanical ventilation usually have shunts in the range of 20% to 50%. Increased right-to-left shunt is the cause of the difficulty in reversing hypoxemia with supplemental oxygen, even with oxygen concentrations of 100%. For this reason, one goal of ARDS management is to decrease the shunt fraction by reopening (recruiting) alveoli that have no ventilation (i.e., whose $\dot{V}/\dot{Q} = 0$).

LOW COMPLIANCE

Decreased lung compliance in ARDS is due to widespread interstitial and alveolar edema and atelectatic alveoli (microatelectasis). Decreased surfactant activity leads to the collapse of alveoli at end-expiration and increased hysteresis between inspiratory and expiratory pressure-volume curves. Low lung compliance results in low respiratory system compliance. For example, if a patient is on 10 cm H_2O of PEEP and has a normal respiratory system compliance of 100 mL/cm H_2O, a ventilator-delivered tidal volume of 500 mL would result in 5 cm H_2O end-inspiratory pressure in addition to the PEEP of 10 cm H_2O. Taken together, the sum results in a plateau pressure (Pplat) of 15 cm H_2O (see Figure 2.3, Chapter 2). In contrast, if the patient has ARDS and a respiratory system compliance of 20 mL/cm H_2O (again assuming 10 cm H_2O of PEEP), the same 500 mL tidal volume would result in a 25 cm H_2O addition to the PEEP of 10 cm H_2O, resulting in a Pplat of 35 cm H_2O.

Loss of alveolar surfactant activity contributes to the low lung compliance in ARDS by at least three different mechanisms: (1) edema fluid washes surfactant out of alveolar spaces, (2) injury occurring to alveolar type II pneumocytes compromises surfactant production and secretion, and (3) contact with plasma proteins inactivates surfactant. Although loss of surfactant activity contributes to the physiologic abnormalities and respiratory failure in this phase of ARDS, its relative clinical importance remains unclear because clinical trials of replacement surfactant therapy have not improved mortality.

Although the chest radiograph shows the infiltrates as diffusely uniform, computed tomographic (CT) scans of the lungs of ARDS patients indicate a more patchy distribution of fluid and atelectasis. CT scans of patients with ARDS performed at varying inspiratory pressures indicate that alveoli can be divided into three compartments: (1) completely filled and nonrecruitable alveoli, (2) atelectatic and recruitable alveoli, and (3) open alveoli (Figure 73.1). Some have regarded the recruitable and open alveoli as a "baby lung," because they constitute a small fraction of the total lung. Lung protective strategies, such as low tidal volume ventilation, as described later, are based in part on the concept that in patients with ARDS, one is really ventilating a lung for which traditional larger sized tidal volumes (10 to 12 mL/kg predicted body weight) are much too large, resulting in alveolar overdistention and lung injury.

INCREASED MINUTE VENTILATION

Patients with ARDS have increased minute ventilation. This results from marked increases in alveolar dead space, arising from microscopic level changes in ventilation-perfusion ($\dot{V}/\dot{Q}$) ratios that increase the number of alveoli with $\dot{V}/\dot{Q}$ greater than 1. Overall dead space to tidal volume (V_D/V_T) ratios are commonly in the 0.7 to 0.8 range (compared with a normal V_D/V_T ratio of 0.3). As a result, the minute ventilation must be increased two to three times in order to keep the $Paco_2$ in the normal range (see Appendix B). During mechanical ventilation this requires high inspiratory flow rates to maintain an I:E of < 1. Although high respiratory rates are needed to keep $Paco_2$ in the normal range while simultaneously using low tidal volume ventilation, this

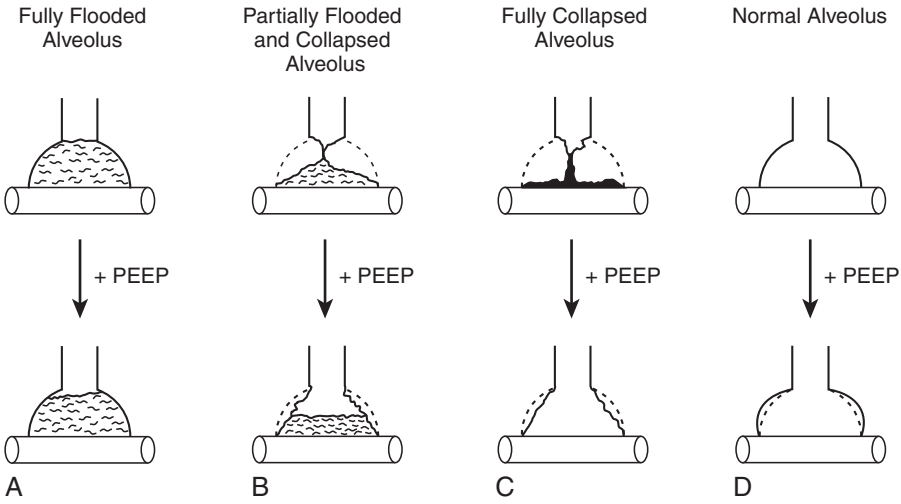


Figure 73.1 Schematic of effects of positive end-expiratory pressure (PEEP) on recruitable and nonrecruitable regions of lungs with ARDS. Alveoli B and C represent the recruitable lung units. Completely fluid-filled alveoli **(A)** are nonrecruitable because PEEP cannot open such alveoli. Likewise, completely normal alveoli **(D)** are also considered to be nonrecruitable because the PEEP-induced increase in their resting volume represents alveolar overdistention. *(From Lanken PN: Adult respiratory distress syndrome: clinical management. In Carlson RW, Geheb MA [eds]: The Principles and Practice of Medical Intensive Care. Philadelphia: WB Saunders, 1991.)*

approach can be limited by short exhalation times and dynamic overinflation (auto-PEEP; see Chapter 2). Therefore, many clinicians allow $Paco_2$ to rise (permissive hypercapnia), prioritizing lung protective ventilation over maintaining normal levels of $Paco_2$.

Clinical Management: Specific Therapy

Specific therapy for ARDS is directed against the cause of the ARDS, such as an antibiotic against an infection causing diffuse pneumonia, or against one or more steps in its pathogenic mechanism, such as an agent that blocks a crucial step in lung inflammation or fibrosis. In contrast, *supportive therapy* includes everything else that is done for ARDS patients.

Specific therapy for early-phase ARDS is limited except in cases involving treatable infections or ARDS resulting from diffuse pulmonary hemorrhage (see Chapter 78). There remains controversy regarding the role of systemic corticosteroids in late-phase persistent ARDS because of inconsistent effects on mortality and concern for side effects. Several meta-analyses comparing high doses of systemic corticosteroids to placebo in patients with ARDS have drawn conflicting conclusions with the majority failing to find a mortality benefit to steroids. Thus, they are not recommended for routine use. In contrast, a much lower daily dose of corticosteroids has become accepted therapy for patients with pneumocystis pneumonia caused by human immunodeficiency virus. Other anti-inflammatory agents have shown promise in animal studies or in preliminary human studies, but confirmation of their efficacy by large, multicenter, controlled clinical trials is lacking. Various other specific therapies targeting pathogenic mechanisms in ARDS, such as statins, are currently under evaluation in clinical trials. Therefore, the current approach to ARDS management focuses on various supportive therapies aimed at improving oxygenation and ventilation and limiting the deleterious affects of mechanical ventilation.

Clinical Management: Supportive Therapy

MECHANICAL VENTILATION

Virtually all patients with ARDS need endotracheal intubation and mechanical ventilation for their survival. The goal of mechanical ventilation is to maintain adequate ventilation and arterial oxygenation in a patient (with a target Pao_2 of 55 to 80 mm Hg; Box 73.2) breathing nontoxic oxygen concentrations (usually assumed to be in the 50% to 60% range) while protecting the lung from ventilator induced lung injury (VILI).

LOW TIDAL VOLUME VENTILATION STRATEGY

Based on the evidence that high alveolar distending pressures and large tidal volumes can perpetuate lung injury, a multicenter randomized controlled clinical trial, conducted by the National Institutes of Health ARDS Network and published in 2000, tested the efficacy and safety of a low tidal volume ventilation strategy in ARDS. The strategy used in the trial was volume-controlled ventilation in the assist-control mode with a tidal volume of 6 mL/kg predicted body weight (PBW) (see Box 73.2). If the Pplat at this tidal volume was ≤ 30 cm H_2O, the patient continued to receive the 6 mL/kg PBW tidal volume. If the Pplat exceeded 30 cm H_2O, however, the tidal volume was lowered stepwise until the Pplat dropped below 30 cm H_2O or the tidal volume reached a minimum of 4 mL/kg PBW (whichever occurred first). Respiratory rates were increased up to 35 breaths/minute to treat associated respiratory acidosis, although relative (permissive) hypercapnia was tolerated. PEEP and FIo_2 were set according to a uniform protocol derived from the clinical practices used in the participating ICUs (see Box 73.2).

This low tidal volume ventilation strategy was compared with a traditional tidal volume ventilation strategy in which patients were also managed in the assist/control mode but at tidal volumes of 12 mL/kg PBW. If Pplat at this tidal volume was ≤ 50 cm H_2O, no change in tidal volume was made. If Pplat exceeded 50 cm H_2O, however, the tidal volume was reduced until Pplat fell below 50 cm H_2O or until the tidal volume reached 4 mL/kg PBW (whichever occurred first).

This study tested the hypothesis that small tidal volume ventilation would result in lower mortality for patients with ALI and ARDS. Ventilating at low tidal volumes hypothetically should decrease the degree of alveolar overdistention and associated alveolar injury. The clinical trial was stopped early after 861 patients were enrolled when a statistically significant decrease in hospital mortality was noted in the low tidal volume strategy group. The mortality fell from 39.8% in the traditional tidal volume group to 31% in the low tidal volume group, representing a 22% relative decrease in mortality. This study's protocol is summarized in Box 73.2.

Currently low tidal volume lung protective ventilation should be the standard initial approach to patients with ARDS and is the only ventilator-related therapy to demonstrate a consistent mortality benefit. Challenges can arise from low tidal volume ventilation including ventilator asynchrony and relative hypercapnia, particularly in the setting of the high V_D/V_T ratios common in ARDS. Hypercapnia can first be addressed by increasing the respiratory rate while maintaining low tidal volumes. If increases to the respiratory rate become limited by inadequate expiratory time and dynamic hyperinflation (auto-PEEP), permissive hypercapnia is generally tolerated until the patient's arterial pH drops to as low as 7.15 (see Box 73.2). Ventilator asynchrony is generally addressed by increasing sedation (Chapter 5) and, in some cases, initiating pharmacologic paralysis (Chapter 6).

POSITIVE END-EXPIRATORY PRESSURE

Mechanism of Action

Positive end-expiratory pressure improves arterial oxygenation and decreases right-to-left shunt in most patients with ARDS. PEEP increases the end-expiratory position of the lungs (functional

BOX 73.2 ■ Summary of NIH NHLBI ARDS Network Low Tidal Volume Ventilation Protocol Used in the "ARMA" Clinical Trial

Part I. Ventilator Setup and Operational Orders

1. Calculate predicted body weight (PBW). (Use formulas below* or see tables in Appendix E.)
2. Use assist control ventilatory mode and set tidal volume (V_T) to 8 mL/kg PBW (if patient's V_T > 8 mL/kg).
3. Reduce V_T by 1 mL/kg PBW at 2 hour intervals or less until V_T = 6 mL/kg PBW.
4. Set initial respiratory rate (RR) to equal patient's prior $\dot{V}_E$ (with RR < 36 bpm).
5. Adjust V_T and RR to meet pH and plateau pressure (Pplat) goals below if possible.
6. Set inspiratory flow rate above patient demand (usually > 80 L/min); adjust flow rate to set I:E ratio of 1:1.0–1.3 if possible.

Part II. Oxygenation Goal: Pao_2 = 55–80 mm Hg or Sao_2 = 88%–95%

1. Use these following "steps" of Fio_2-PEEP to achieve oxygenation goal:

Step	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Fio_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12
Step	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*
Fio_2	0.7	0.8	0.9	0.9	0.9	1.0	1.0	1.0
PEEP	14	14	14	16	18	20	22	24

Part III. Plateau Pressure (Pplat) Goal: ≤30 cm H_2O

1. Check Pplat (by using 0.5-sec inspiratory pause), Sao_2, RR (total), V_T, and ABG (if available) every 4 hours (or more frequently if available) and after any changes in PEEP or V_T.
2. If Pplat > 30 cm H_2O, decrease V_T by 1 mL/kg steps (to a minimum of 4 mL/kg PBW).
3. If Pplat < 25 cm H_2O and V_T < 6 mL/kg PBW, increase V_T by 1 mL/kg until Pplat > 25 cm H_2O or V_T = 6 mL/kg PBW.
4. If Pplat < 30 cm H_2O and if patient has breath stacking (so-called "double-clutching"—indicating patient-ventilator asynchrony [see Chapter 47])—one may increase V_T in 1 mL/kg PBW increments (to a maximum of 8 mL/kg PBW as long as Pplat ≤ 30 cm H_2O).

Part IV. pH Goal: 7.30–7.45

Acidosis Management: pH < 7.30

1. If pH = 7.15–7.30, increase RR until pH > 7.30 or $Paco_2$ < 25 mm Hg (maximum RR = 35/min due to potential for auto-PEEP [see Chapter 2]); if RR = 35/min and $Paco_2$ < 25 mm Hg, may give intravenous (IV) sodium bicarbonate ($NaHCO_3$).
2. If pH < 7.15 and $NaHCO_3$ considered or infused, V_T may be increased in 1 mL/kg PBW steps until pH > 7.15 (i.e., Pplat goal may be exceeded due to life-threatening acidosis).

Alkalosis Management: pH > 7.45

Decrease RR if possible.

Adapted from The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308, 2000. (Complete protocol is available from www.ardsnet.org).

**Male PBW = 50 + 2.3 (height [inches] – 60); female PBW = 45.5 + 2.3 (height [inches] – 60). See Appendix E for tables of PBW for men and women according to height.*

ABG, arterial blood gas; ARDS, acute respiratory distress syndrome; ARMA, acute respiratory management of ARDS; bpm, breaths per minute; I:E, inspiratory-to-expiratory; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; PBW, predicted body weight; PEEP, positive end-expiratory pressure; RR, respiratory rate on ventilator; q4h, every 4 hours; Sao_2, oxygen saturation by pulse oximetry; V_T, tidal volume; $\dot{V}_E$, minute ventilation.

residual capacity) by reinflating completely atelectatic alveoli and expanding alveoli that are partially atelectatic or open (Figures 73.1). By decreasing the number of alveoli with $\dot{V}/\dot{Q}$ ratios of zero or nearly zero, PEEP decreases the shunt fraction and, hence, improves oxygenation. In addition, through its lung recruitment effects, PEEP may improve respiratory system compliance.

PEEP should generally be applied in increments of 2 to 3 cm H_2O and in combination with stepwise increases in F_{IO_2} as shown in Box 73.2. In this approach, the degree of PEEP-induced lung recruitment is reflected by improvement in P_{aO_2}. Although increasing PEEP raises the P_{aO_2} in most cases of ARDS, high PEEP may reduce cardiac output by decreasing venous return to the thorax ("central tourniquet effect"). This reduction in cardiac output can usually be reversed by infusions of inotropic agents or by intravascular volume expansion, although the latter may create more lung edema.

In general, after the target P_{aO_2} has been reached and oxygenation has improved, F_{IO_2} and PEEP can be lowered stepwise in small decrements (see Box 73.2). The abrupt removal of PEEP may result in a precipitous fall in P_{aO_2}, which can take hours to fully recover. For the same reason, a closed system should be used for all tracheal suctioning (that should be minimized).

Patients may "derecruit" alveoli rapidly if disconnected from the ventilation during transport or during tracheal suctioning. In these circumstances, in order to open collapsed alveoli, ICU clinicians may utilize recruitment maneuvers (RMs). When doing a RM, a respiratory care practitioner applies a sustained high level of continuous positive airway pressure (CPAP) that may be repeated once or twice after a short interval. Common RM parameters are CPAP at 30 cm H_2O for a duration of 30 seconds (so-called "30-30" RM) or CPAP at 40 cm H_2O for 40 seconds ("40-40" RM). These are generally effective in restoring oxygenation that was compromised with decruitment and generally well tolerated. However, RMs may induce transient hypotension, desaturation, and bradycardia in some patients, especially if they are relatively hypovolemic.

Higher versus Traditional Levels of PEEP

Several studies have been conducted comparing a high-PEEP and a traditional or low-PEEP strategy in ARDS. The NIH ARDS Network conducted a study of two protocolized approaches to setting PEEP levels in patients receiving low tidal volume ventilation. In their study (ALVEOLI), PEEP levels were set based on tables of predetermined combinations of PEEP and F_{IO_2} with patients randomized to either a lower or higher PEEP strategy. This study failed to demonstrate a mortality benefit to one PEEP strategy over the other. In a meta-analyses of several similar studies, the high PEEP strategies still failed to demonstrate an improvement in mortality but appeared to reduce the need for rescue therapies for severe hypoxemia and the incidence of dying from severe hypoxemia.

Some have advocated that PEEP should be set at a level determined by measurements of lung recruitment. This is achieved by first measuring the patient's static pressure-volume (P-V) curve. Then, one identifies the lower inflection point (see Figure 73.2) and sets PEEP at a level just above this point. Unfortunately, this method can be challenging in practice as such static P-V curves often do not show clear, reproducible lower inflection points and can change regularly, requiring repeated determinations (that often requires paralysis). The combination of sufficient PEEP to exceed the lower inflection point and ventilation with a tidal volume small enough so as not to exceed the upper inflection point of the P-V curve (see Figure 73.2) has been referred to as the "open lung" strategy and is the goal of lung protective ventilation.

ALTERNATIVE METHODS OF MECHANICAL VENTILATION

Pressure Control and Inverse Ratio Ventilation

Pressure control (PC) ventilation is another method of limiting alveolar pressure. PC allows for the target pressure to be set and maintained at a pressure that limits both the peak and plateau

pressures seen by the lung. The tidal volume delivered at this set pressure depends on the compliance of the lung (plus chest wall) and, therefore, is variable particularly in patients with ARDS. PC can be used as a reasonable alternative to the assist-control (A-C) (volume-cycled) mode that was used by the ARDS Network in the ARMA clinical trial (see Box 73.2). However, when using PC ventilation in a nonsalvage mode, one must keep in mind that the end-inspiratory alveolar pressure (equivalent to Pplat in A-C mode) is the sum of the set inspiratory pressure (IP) plus the applied PEEP plus auto-PEEP, if any. For example, if PEEP = 10 cm H_2O, and

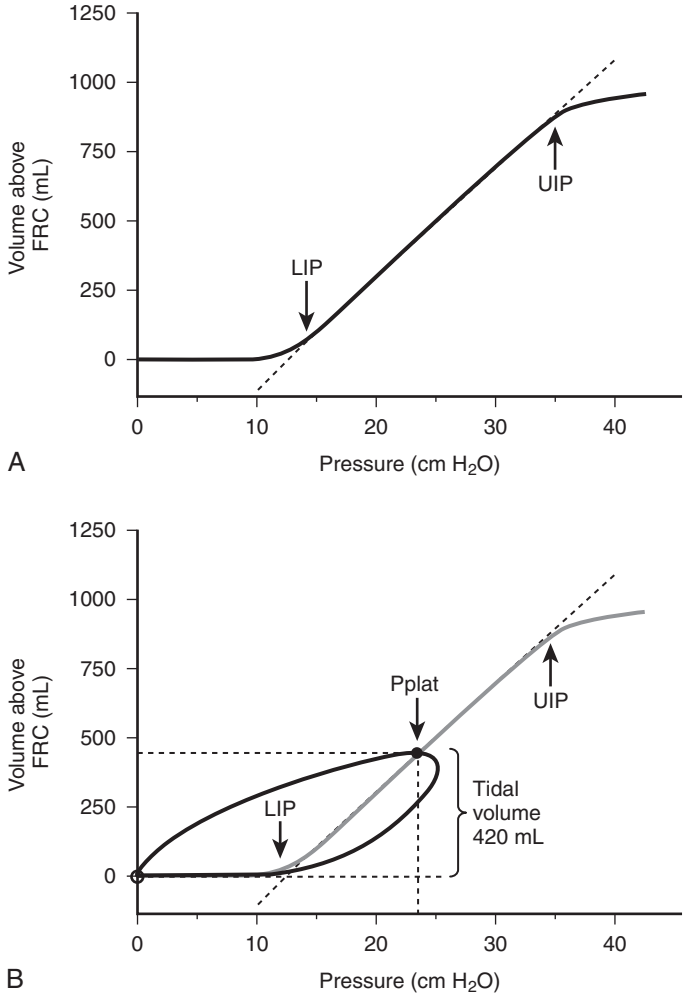


Figure 73.2 **A,** Schematic inspiratory static pressure-volume (P-V) curve of the respiratory system (lung and chest wall combined) in ARDS with a lower inflection point (LIP) at ~12-14 cm H_2O and an upper inflection point (UIP) at ~35 cm H_2O. The x-axis is recoil pressure of the respiratory system, and the y-axis is lung volume above functional residual capacity (FRC). **B,** Same static P-V as in **A,** plus a dynamic P-V curve of a tidal volume (V_T) of 420 mL (V_T = 6 mL/kg predicted body weight [PBW] × 70 kg PBW = 420 mL) with an end-expiratory volume *(open circle)* at PEEP = 0, which is far below the LIP (suggesting an increased risk from repetitive opening and closing [i.e., atelectrauma]). This tidal volume results in an end-inspiratory or plateau pressure (Pplat) of 23 cm H_2O *(closed circle)*, which is below the UIP.

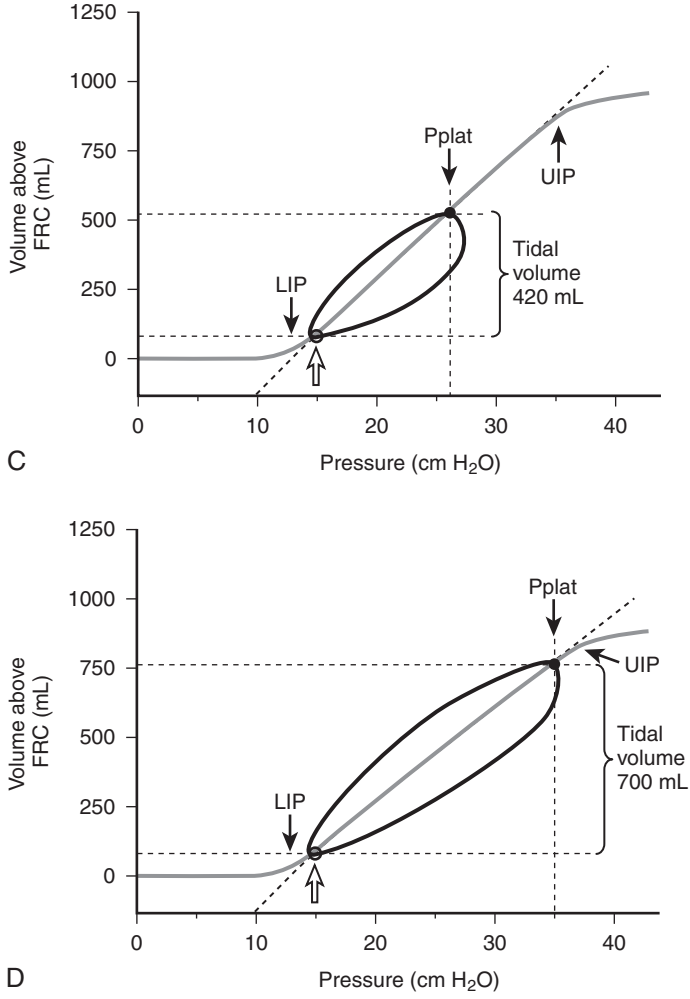


Figure 73.2 cont'd, **C,** Dynamic P-V curve for the same 420 mL tidal volume as in **B** with PEEP increased to 15 cm H_2O, which moves the end-expiratory volume *(open circle)* up the static P-V curve to a new FRC *(open arrow)*, which is now slightly above the LIP. This tidal volume and PEEP combination results in a Pplat of ~27 cm H_2O *(closed circle)*, which is still below the UIP as well as the upper limit of Pplat of 30 cm H_2O used in the ARDSNet low tidal volume ventilation study (see Box 73.2). **D,** Dynamic P-V curve of a 700-mL tidal volume (10 mL/kg PBW for the same 70 kg PBW), starting at the same 15 cm H_2O PEEP *(open arrow)* and resulting in a Pplat of 35 cm H_2O. The 700 mL tidal volume's Pplat is above the 30 cm H2O cutoff for Pplat in the ARDSNet study (see Box 73.2) as well as being near the UIP in this schematic. The latter implies a greater extent of alveolar overdistention that increases the risk for ventilator-induced lung injury (see text). ARDSNet, NIH NHLBI ARDS Clinical Trials Network.

IP = 25 cm H_2O to produce a tidal volume of 6 mL/kg PBW, the patient's end inspiratory pressure would be 35 cm H_2O. Because the latter exceeds the threshold of a Pplat 30 cm H_2O that was used in the ARDS Network ARMA trial for decreasing tidal volume to 5 mL/kg PBW (see Box 73.2), the IP should be decreased such that tidal volume is 5 mL/kg PBW and IP + applied PEEP ≤ 30 cm H_2O.

Airway Pressure Release Ventilation

Airway pressure release ventilation (APRV) is an alternative mode of ventilation that some ICU practitioners use in salvage and nonsalvage situations (Chapter 74). However, controlled clinical trials are lacking that show that APRV is equal to or superior to the ARDS Network's low tidal volume ventilation strategy in terms of survival benefit or safety.

High-Frequency Oscillatory Ventilation

High-frequency oscillatory ventilation (HFOV) is another alternative mode of ventilation in which patients are ventilated with rapid pressure oscillations generating very small tidal volumes while a relatively constant airway pressure is applied to maintain alveolar recruitment. Theoretically, HFOV is the ultimate low stretch mode of ventilation, as its tidal volumes are commonly in the 50 to 200 mL range. Whereas HFOV is routinely used in neonatal ICUs for severe respiratory distress syndrome of the newborn, its use in adults with ARDS has been limited to centers with the specialized oscillating ventilator and clinical and technical expertise necessary to use it safely. Previous small clinical trials have demonstrated the technical feasibility of the method and improvements in oxygenation when compared to conventional approaches but were underpowered to test for a mortality benefit. However, a large multinational, multicenter randomized controlled trial (OSCILLATE trial) comparing HFOV to low tidal volume ventilation at high PEEP to treat early moderate to severe ARDS was stopped early in August 2012 due to statistically significantly higher number of deaths in the group that received HFOV. Pending further published results, the early stopping of the OSCILLATE trial will discourage the use of HFOV in early severe ARDS (i.e., non-salvage use).

RESCUE THERAPIES FOR REFRACTORY HYPOXEMIA

In some patients, ARDS progresses to life-threatening refractory hypoxemia despite standard mechanical ventilation with high F_{IO_2} and PEEP. Various rescue therapies can improve and maintain acceptable oxygenation in many of these patients, including the alternative methods of mechanical ventilation discussed previously. Although these methods have been demonstrated to improve oxygenation, none has been shown to improve mortality. Because there are limited data for one rescue therapy over another, the choice of rescue therapies should be based on available technologic and clinical expertise, cost, and the goals of care.

Prone Positioning

Various studies have described improvements in oxygenation with the use of prone positioning. The rationale behind this method is based on the CT findings in ARDS that show localization of lung water in the dependent parts of the lung (i.e., posteriorly in supine patients). It was hypothesized that turning a patient from supine to prone would result in less right-to-left shunt through the fluid-filled alveoli because the prone position gas-filled alveoli would now be in the dependent parts of the lung. Most studies find that the technique results in improved P_{AO_2} in a majority of patients with ARDS but no mortality benefit. Likewise, in most patients who are "proned," the improvement in oxygenation is temporary and may respond to repeated turning. In a meta-analysis of various clinical trials, prone positioning failed to demonstrate a mortality benefit in the overall treatment group but suggested a possible mortality benefit in those with severe ARDS ($P_{AO_2}/F_{IO_2} \leq 100$). The results of this post-hoc analysis using the Berlin definition of severe ARDS await confirmation by a prospective controlled clinical trial of proning in this subgroup of ARDS patients. Complications of this method are not uncommon and include loss of airway during the turning and pressure ulcers on the chin and face if the prone position is continued for prolonged periods.

Inhaled Nitric Oxide and Epoprostenol (Prostacyclin)

Like prone positioning, inhaled nitric oxide (NO) has been reported to result in a temporary improvement in oxygenation. Because NO leads to relaxation of smooth muscle, it is hypothesized that inhaled NO functions as a selective vasodilator that affects only those alveoli that are ventilated. By this action, it selectively increases blood flow to these ventilated alveoli by lowering arteriolar resistance, while having no effect on nonventilated alveoli. The selective vasodilation and increased blood flow to ventilated alveoli result in significant improvements in $\dot{V}/\dot{Q}$ matching and therefore oxygenation. In addition, it has no systemic effects because its effects dissipate quickly after combining with hemoglobin.

Several clinical trials comparing NO inhalation with conventional mechanical ventilation have been performed, including a trial in 177 patients with ARDS indicating that NO inhalation improved Pao_2 in ~60% of enrolled patients but its effects were transient. None found improvements in mortality or a shortened duration on the ventilator in the NO-treated group.

In the United States, some ICUs use NO for selected patients with severe ARDS as part of their salvage therapy package. Although NO seems to have little toxicity when it is properly administered, tolerance to the inhaled NO develops so that severe hypoxemia can result if the delivery of NO were to stop abruptly. Also, the high cost of inhaled NO has limited its use. Although clinical trial evidence is also lacking to support its efficacy, inhaled prostacyclin (prostaglandin I2) (its FDA-approved name is epoprostenol), another selective pulmonary vasodilator, has been suggested as a lower-cost alternative to NO and is used is some centers.

Neuromuscular Blocking Agents

Neuromuscular blocking agents (NBAs) are frequently used in severe cases of ARDS to promote ventilator synchrony and improve oxygenation when sedation alone is inadequate (Chapter 6). Despite their frequent use, controversy exists over the role of NBAs in ARDS. One concern is that their use is associated with an increased risk of diffuse critical illness myopathy that may result in a prolonged neuromuscular weakness in survivors of ARDS (Chapter 48). Although several randomized controlled trials have demonstrated improvements in oxygenation with the use of neuromuscular blocking agents, Papazian et al reported in 2011 the results of a multicenter randomized controlled trial of 340 patients with moderate to severe ARDS ($Pao_2/Fio_2 < 150$): the group that received an initial 48 hours of paralysis by a cisatracurium infusion had a lower adjusted 90-day mortality rate compared to the control arm, which received a placebo infusion plus heavy sedation. This study reported an unadjusted 90-day mortality rate of 31.6% in the cisatracurium group and 40.7% in the control group, and this difference was statistically significant only after adjusting for differences between groups at baseline in Pao_2/Fio_2, baseline Pplat, and the Simplified Acute Physiology II score. Furthermore, the rates of ICU-acquired paresis did not differ significantly between the two groups. Because evidence is lacking that NBAs have in vitro anti-inflammatory actions by themselves, some hypothesize that NBAs allowed better adherence to the ARMA protocol as a mechanism to explain their reported efficacy. Further studies are needed to confirm the reported efficacy and safety of early neuromuscular blockade before its routine use can be recommended.

Extracorporeal Methods of Gas Exchange

Although limited by local availability and cost, there has been renewed interest in extracorporeal methods to provide oxygenation or carbon dioxide removal to treat select patients with severe ARDS. Extracorporeal membrane oxygenation (ECMO) is a therapy that relies on an external artificial membrane and a mechanical pump to provide gas exchange and maintain systemic perfusion when a patient's native heart or lung function is inadequate. In venovenous ECMO, the most common form of ECMO used in patients with ARDS, blood is removed via a large venous catheter in a central vein, passed through an external membrane that oxygenates and removes carbon

Pressure-Control-Inverse Ratio Ventilation (PC-IRV)

In the past, PC was often used as a "salvage" mode in the face of deteriorating oxygenation in severe ARDS (Figure 73.E1). In this situation, PC utilized inverse ratio ventilation (IRV), in which the "inverse ratio" refers to an inspiratory time to expiratory time (I:E) ratio that is < 1. Conventional I:E ratios of 1:3 to 1:1 provide time for passive expiration to facilitate blood return to the heart. In pressure control inverse ratio ventilation (PC-IRV), inspiration is deliberately prolonged so that it exceeds expiration by 50% to 400%. This results in an increased mean airway pressure compared with conventional mechanical ventilation utilizing the same pressure limit because patients spend a longer part of the respiratory cycle in inspiration. Increases in mean airway pressure can translate into increases in Pao_2.

A concern of PC-IRV is that the method often "stacks" tidal volumes because there is insufficient time for the complete exhalation of the preceding breath. Dynamic hyperinflation (increased functional residual capacity) results in and is reflected by the presence of auto-PEEP, an elevated end-expiratory alveolar pressure caused by elastic recoil of incompletely emptied alveoli. Although dynamic hyperinflation can initially result in improvements in oxygenation, there is the potential for hemodynamic compromise as a result of higher mean airway pressures and increased risk of barotrauma or ventilator-induced lung injury as a result of high alveolar pressures. In addition, IRV almost always necessitates heavy sedation and often paralysis of the patient. Controlled clinical trials are lacking that support improvements in mortality with PC-IRV or the superiority of PC-IRV to low tidal volume mechanical ventilation in efficacy or safety in therapy of ARDS.

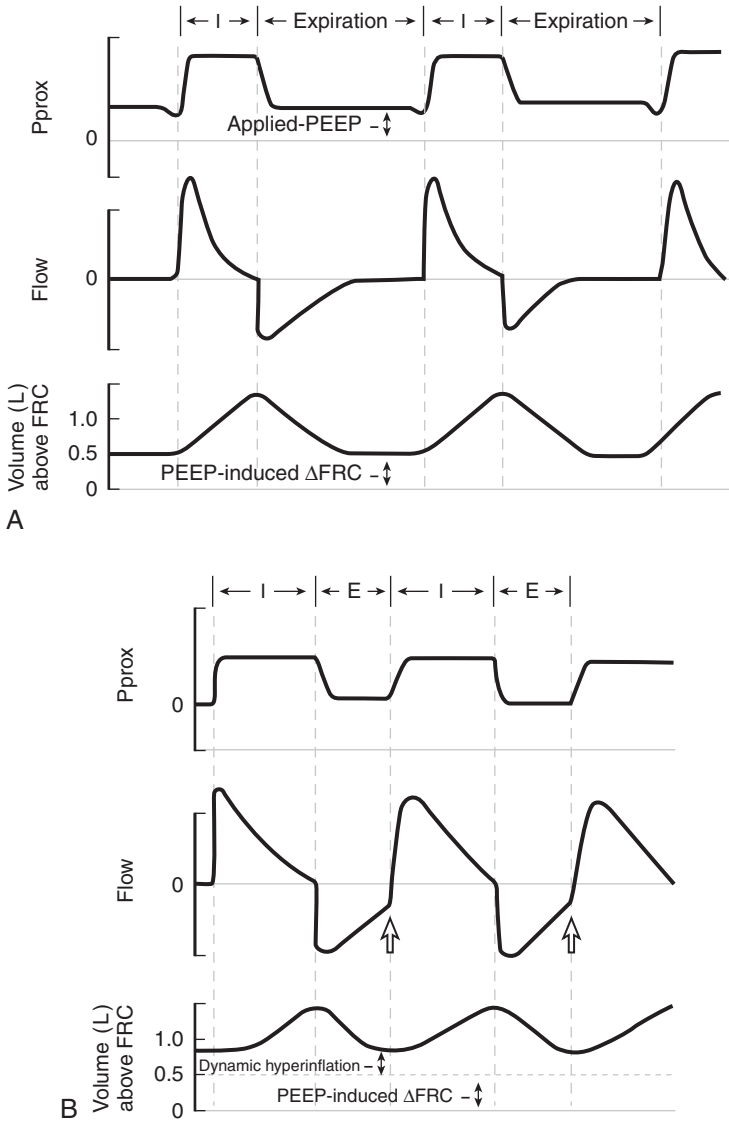


Figure 73.E1 Schematic pressure, flow, and volume waveforms during pressure control ventilation (PCV) with applied positive expiratory pressure (PEEP). **A,** The inspiratory-to-expiratory (I:E) time is 1:2. The pressure waveform resembles the pressure support mode with the patient triggering each breath (see Figure 2.5, Chapter 2) but with a marked decelerating flow pattern. The applied PEEP increases the functional residual capacity (FRC) by 500 mL (PEEP-induced ΔFRC). **B,** In pressure-controlled inverse ratio ventilation (PC-IRV), the I:E time is "reversed," with I > E. Because of this, the next ventilator-delivered breath starts before expiratory flow has returned to zero *(open arrows)*, resulting in auto-PEEP and dynamic hyperinflation of 300 mL. The latter is in addition to the increased FRC resulting from the applied PEEP (PEEP-induced ΔFRC). The patient is not initiating any breaths. E, expiration; I, inspiration; PEEP, positive end-expiratory pressure; Pprox, pressure at the proximal end of the endotracheal tube.

dioxide from the blood, and then returned to the venous circulation (Chapter 88). However, risks of ECMO are substantial and include a risk of bleeding secondary to the need for anticoagulation, vascular injury, and catheter-related bloodstream infection.

Although ECMO has been available for decades, the therapy attracted renewed attention during the H1N1 influenza pandemic of 2009. Prior to the pandemic, two randomized controlled trials from 1979 and 1994 failed to demonstrate a mortality benefit from the use of ECMO or extracorporeal CO_2 removal ($ECCO_2R$) for severe ARDS. Since that time, technologic advances have been made, prompting renewed use of ECMO during the influenza pandemic as young otherwise healthy patients developed ARDS with refractory hypoxemia.

In 2012, the Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial in the United Kingdom reported encouraging results. In this trial, patients were transferred to a central specialized center for consideration of ECMO. CESAR enrolled 180 patients with severe but potentially reversible respiratory failure. Of the patients randomized to be referred to the ECMO center, 76% ultimately underwent ECMO. The primary outcome, death or severe disability at 6 months, occurred in 37% of the patients referred to the ECMO center and 53% of those in the usual treatment arm, a statistically significant finding. However, how to interpret these results remains uncertain because one cannot distinguish the effects of the ECMO intervention from those of other differences in overall care at the specialized referral center. While ongoing trials attempt to address the use of ECMO in patients with ARDS, specialized centers continue to use ECMO for severe ARDS with refractory hypoxemia in a highly selective population of patients.

HEMODYNAMIC, FLUID, AND DIURETIC THERAPY

Diuretics and fluid restriction are commonly used to lower pulmonary capillary pressures in patients with ARDS, preventing further pulmonary edema in the setting of increased permeability. In patients with ARDS and MOSF, however, decreasing intravascular volume is usually limited by hypotension, low cardiac output, and impaired organ perfusion. Although ARDS patients with a more positive fluid balance have been reported to have worse outcomes in observational studies, the more positive fluid balance might have been a marker, rather than a cause, of those with worse prognoses. To address the issue of fluid balance in ARDS, the ARDS Network conducted a randomized clinical trial (the Fluid and Catheter Treatment Trial [FACTT]) in 1000 patients with ALI or ARDS. Patients were randomized to a conservative or a liberal strategy of fluid management based on explicit protocols. Patients enrolled in the conservative strategy had up to 2 fewer days free from mechanical ventilation and spent fewer days in the ICU during the first 28 days after enrollment, both statistically significant results. However, neither hospital length of stay nor mortality was statistically different between groups. A note of caution was raised, however, when a prospective study of a subset of FACTT survivors, albeit small in number and needing confirmation, found an increased risk of cognitive dysfunction at 12 months after hospital discharge in those randomized to the fluid conservative group as an independent risk factor in multivariate analyses.

Although monitoring of intravascular volume by measuring pulmonary artery wedge pressures has been previously used in the treatment of ARDS patients, the use of the pulmonary arterial catheter has been reported to be a risk factor for increased mortality in several groups of ICU patients. In the same randomized trial of conservative versus liberal fluid management (FACTT), subjects were also randomized to receive hemodynamic management guided by a pulmonary artery (PA) catheter versus a central venous catheter (CVC). This study failed to demonstrate improvements in any outcomes with PA catheter–guided therapy. The PA catheter group also had more than twice as many catheter-related complications, predominately arrhythmias. Based on these findings and others, routine use of pulmonary artery catheters in ARDS is not recommended.

GENERAL ICU SUPPORTIVE CARE

Even prior to the mainstream acceptance of lung protective ventilation, the survival of patients with ARDS appeared to improve dramatically, with mortality rates falling from 40% to 60% in the 1980s to 30% to 40% in the 1990s. This mortality trend in the absence of a "magic bullet" to treat ARDS suggests that improvement in general ICU supportive care may have resulted in the better outcomes. Several studies have demonstrated a continued improvement with the widespread use of lung protective mechanical ventilation. Patients with ARDS require comprehensive supportive care. This includes intensive nursing and respiratory care; prophylaxis against stress-related gastric erosions and deep venous thromboses (Chapter 12); early detection and management of life-threatening barotrauma (Chapter 35); replacement therapy for renal and other organ failure (Chapter 20); aggressive nutritional therapy (Chapter 15); and prevention, early diagnosis, and treatment of nosocomial infections (Chapters 11, 14, and 18).

Long-Term Sequelae in Survivors

Most patients with ARDS who are weaned from mechanical ventilation have a good prognosis for continued recovery of lung function (e.g., most patients have no clinically significant residual lung damage after 1 year). However, many survivors have long-term physical deficits, cognitive dysfunction, and emotional distress. These adverse outcomes result from the effects of their critical illness, prolonged ICU hospitalization, and comorbid conditions but without a clear understanding of their pathophysiologic mechanism. Improved understanding of those mechanisms and improving long-term quality of life, including cognitive and psychological functioning, must be important goals of future clinical investigation and clinical trials.

An annotated bibliography can be found at www.expertconsult.com.

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This meta-analysis of clinical trials on proning in ARDS demonstrated improved oxygenation but not improved mortality among patients treated with proning.

Acute Respiratory Distress Syndrome Network: Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 354:2564-2575, 2006.

This randomized clinical trial of 1000 patients with acute lung injury/ARDS compared a protocolized conservative to a liberal fluid strategy. Although there was no significant difference in the primary mortality outcome, patients using the conservative strategy had a shortened duration of mechanical ventilation and days in the intensive care unit.

Acute Respiratory Distress Syndrome Network: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 354:1671-1684, 2006.

This is a randomized clinical trial of 180 patients with ARDS of at least 7 days in duration, randomized to methylprednisolone or placebo. The primary end point of mortality was not different between groups.

Acute Respiratory Distress Syndrome Network: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 351:327-336, 2004.

This randomized clinical trial of 549 patients with acute lung injury and ARDS failed to demonstrate differences in mortality outcomes between protocols with lower and higher PEEP goals.

Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301-1308, 2000.

This multicenter randomized, controlled clinical trial of 861 patients with acute lung injury and acute respiratory distress syndrome shows that a low tidal volume ventilation strategy (summarized in Box 73.2) significantly decreased mortality (from 39.8% to 31.0%, P = 0.007).

ARDS Definition Task Force: Acute respiratory distress syndrome: the Berlin definition. JAMA 307: 2526-2533, 2012.

This report described the new "Berlin definition" of ARDS that has been endorsed by the European Society of Intensive Care Medicine, the American Thoracic Society, and the Society of Critical Care Medicine.

Ashbaugh DG, Bigelow DB, Petty TL, Levine BE: Acute respiratory distress in adults. Lancet 2:319-323, 1967.

This article has the classic original description of ARDS and the use of PEEP in its management.

Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS. Am Rev Respir Dis 149:818-824, 1994.

This report has the first consensus criteria for defining acute lung injury and ARDS. The AECC criteria for diagnosing ARDS has been updated and revised by the "Berlin definition."

Davidson TA, Caldwell ES, Curtis JR, et al: Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. JAMA 281:354-360, 1999.

In this case control study, survivors of ARDS had clinically significant reductions in health-related quality of life that seemed to be caused by their ARDS and its sequelae (compared with matched controls of patients with trauma or sepsis without ARDS).

Ferguson ND, Cook DJ, Guyatt GH, et al: High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med 2013. DOI: 10.1056/NEJMoa1215554.

This large multicenter randomized controlled clinical trial (RCT), named the OSCILLATE study, compared high-frequency oscillatory ventilation (HFOV) to lower tidal volume with high PEEP group of patients with early ARDS. It was stopped early due to increased mortality in the HFOV group compared to the control group.

Gattinoni L, Pesenti A, Bombino M, et al: Relationships between lung computed tomographic density, gas exchange and PEEP in acute respiratory failure. Anesthesiology 69:824-832, 1988.

This classic article described heterogeneous distribution of fluid in the lung in ARDS and the effects of PEEP.

Herridge MS, Tansey CM, Matte A, et al: Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 364:1293-1304, 2011.

Follow-up of the 109 survivors of ARDS up to 5 years demonstrated persistent exercise limitation and physical and psychological sequelae after ARDS, despite return to normal or near normal pulmonary function.

Neto AS, Cardoso SL, Manetta JA, et al: Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome. A meta-analysis. JAMA 308:1651-1659, 2012.

This systematic review of 20 published studies that compared use of lower vs. higher tidal volumes in patients without ARDS at the start of mechanical ventilation. It found that lung protective ventilation was associated with better clinical outcomes (i.e., lower risk for development of acute lung injury or mortality).

Papazian L, Forel JM, Gacouin A, et al: Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 363:1107-1116, 2010.

This multicenter randomized trial of 340 patients with severe ARDS ($Pa_{O_2}/F_{I_{O_2}} < 150$) compared 48 hours of cisatracurium to placebo and reported a mortality benefit for the group randomized to cisatracurium.

Young D, Lamb S, Shah S, et al: High-frequency oscillation for acute respiratory distress syndrome. N Engl J Med 2013. DOI: 10.1056/NEJMoa1215716.

This multicenter RCT in the United Kingdom (the OSCAR study) compared HFOV to usual ventilation for patients with ARDS and found no significant differences in outcomes, including mortality.

Zambon M, Vincent JL: Mortality rates for patients with acute lung injury/ARDS have decreased over time. Chest 133:1120-1127, 2008.

This systematic analysis of ARDS literature examined trends in mortality between 1994 and 2006. The study demonstrated a consistent reduction in mortality rates over this time period.

CHAPTER 74

Alternative Modes of Ventilation in Acute Lung Injury

Chirag V. Shah ■ Michael J. Frazer

The purpose of mechanical ventilation in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) is to provide adequate oxygenation and ventilation while minimizing ventilator-induced lung injury (VILI). Clinicians are using alternative (i.e., nonconventional) modes of ventilation with increasing regularity based on sound physiologic rationale and the results of preliminary clinical trials. This chapter describes the fundamentals of *biphasic intermittent positive airway pressure ventilation* (Bi-Level) with a detailed focus on the conceptual underpinnings of *airway pressure release ventilation* (APRV) and the clinical application of these techniques in patients with ALI.

Throughout this chapter the Bi-Level nomenclature refers to the mode of mechanical ventilation that intermittently cycles between two levels of continuous positive airway pressure (CPAP) and allows for spontaneous breaths throughout the entire respiratory cycle. Thus, Bi-Level ventilation is distinct from the biphasic intermittent positive airway pressure (BIPAP) mode used for non-invasive ventilation (Chapter 3). APRV refers to an "open lung" ventilatory strategy, which is a type of Bi-Level mode that places specific constraints on inflation and deflation pressure levels, cycle times, and pressure support (PS) levels during spontaneous breaths (Figure 74.1).

Nomenclature and Description

With Bi-Level ventilation, the respiratory cycle commences at a high CPAP, designated as P high or P_H, for a discrete time period, T high or T_H. The amount of pressure and length of time of this *inflation phase* result in lung recruitment and oxygenation. Each inflation phase is coupled to a *release phase* with a set low pressure, P low or P_L, and duration, T low or T_L, thus completing a respiratory cycle (Figure 74.2). The release phase helps to eliminate CO_2 and provide adequate ventilation. Importantly, integrated within and independent of each ventilatory cycle, the patient is allowed unrestricted spontaneous breaths via an active exhalation valve (AEV). While AEVs are not new, improved technology now allows the AEV in Bi-Level ventilation mode to open slightly for spontaneous respiration while maintaining constant airway pressure. These spontaneous efforts may or may not be assisted with pressure support (PS) (Chapter 2) and can augment oxygenation and ventilation. In essence, Bi-Level uses a high CPAP level to oxygenate with intermittent timed releases to a low CPAP level to achieve alveolar ventilation. Without spontaneous breathing by the patient, the pressure-time waveform of Bi-Level is similar to that of pressure control ventilation. To this end, Bi-Level should be considered a time triggered, pressure-limited, and time-cycled mode of mechanical ventilation. Synchronized versions of Bi-Level are now present that allow for patient triggering and cycling.

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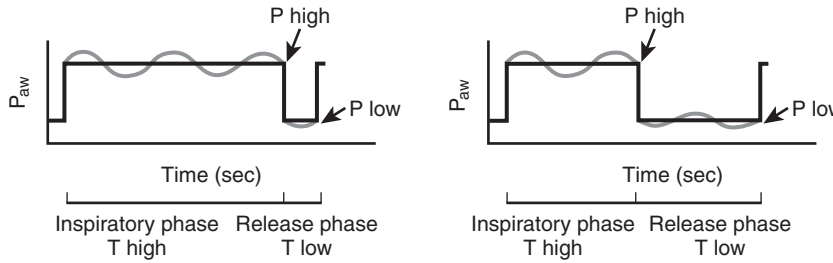


Figure 74.1 Pressure-time graphs of APRV versus standard Bi-Level. APRV is hallmarked by longer inflation phases and brief release phases. Both allow spontaneous breathing (depicted by sinusoidal waves). P_{aw}: airway pressure. *(Adapted from Seymour CW, Frazer M, Reilly PM, et al: Airway pressure release and biphasic intermittent positive airway pressure ventilation: are they ready for prime time? J Trauma 62:1298-1308; discussion 1298-1308, 2007.)*

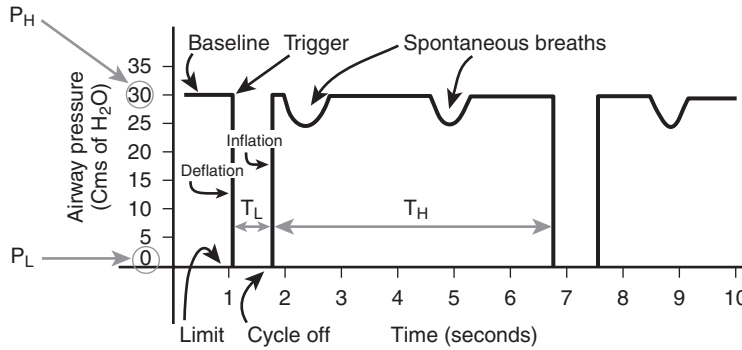


Figure 74.2 Pressure-time graph of APRV. APRV is time triggered, pressure limited, and time cycled. *(Adapted from Frawley PM, Habashi NM: Airway pressure release ventilation: theory and practice. AACN Clin Issues 12:234-246, 2001.)*

Oxygenation during Bi-Level is dependent on the set fraction of inspired oxygen (FiO_2) and the mean airway pressure (P_{aw}), which is mathematically expressed as follows:

$$\text{Mean } P_{aw} = \frac{[(P_H) \times (T_H) + (P_L) \times (T_L)]}{[T_H + T_L]} \qquad \text{(Equation 1)}$$

As will be described later, the mean P_{aw} is typically much higher with APRV than with standard Bi-Level, volume-assist control (VC), or pressure-assist control (PC) modes of ventilation. Minute ventilation (V_E) during Bi-Level is dependent on cycle frequency, changes in lung volumes during respiratory cycles, and the volume and frequency of the patient's spontaneous breaths.

APRV CONCEPT, INDICATIONS, AND POTENTIAL ADVANTAGES

In 1987, Stock et al first described and used APRV in patients with ALI. In the poorly compliant and fluid-filled lungs of ALI patients, the functional residual capacity (FRC) is reduced. In comparison to standard Bi-Level, APRV employs a longer T_H to maximize the generated mean P_{aw} (Equation 1) in an effort to restore FRC to a more favorable position on the pressure-volume curve (see Chapter 73, Figure 73.2). In addition, the timed-release phases in APRV are purposefully short in length and set to a P_L of 0 cm H_2O (see Figure 74.2). Thus, APRV employs high,

but presumably safe, inflation pressures with very brief release (expiratory) phases during which expiratory flow continues until the ventilator starts the next inflation phase.

By creating an expiratory time that is very brief and not allowing the airway pressure to reach 0 cm H_2O, a variable amount of intrinsic positive end-expiratory pressure (iPEEP) is generated (Chapter 2). This iPEEP helps to prevent those lung units recruited during previous inflation cycles from collapsing (de-recruiting) during subsequent release phases as well as decreasing the degree of repetitive opening and closing injury (atelectrauma). The desired iPEEP is attained by increasing or decreasing the expiratory (release) time. Decreasing the T_L will increase the iPEEP and increasing the T_L will decrease the iPEEP.

Expiratory flow is governed by the driving pressure gradient ($P_H - P_L$), the end-inflation lung volume, airway resistance, and the potential energy of the total respiratory system. By maximizing expiratory flow and allowing spontaneous breathing at P_H, adequate CO_2 exchange is still maintained despite an expected drop in total V_E in APRV. Finally, spontaneous breathing during APRV should occur exclusively during the inflation phase when the lung is maximally recruited because the release phases are typically too short in duration to allow spontaneous efforts. This is in contrast to standard Bi-Level when spontaneous breathing is encouraged at both levels of pressure. To avoid potentially injurious pressure levels during the inflation phases, minimal, if any, PS is added to spontaneous breaths on P_H.

Clinical and laboratory studies have also shown that APRV with spontaneous breathing may augment circulatory performance. Active diaphragmatic contraction along with the active development of negative pleural pressure tends to increase venous return and improve cardiac filling.

Finally, the concerns of complications from use of sedatives and neuromuscular blocking agents (NMBAs) in critically ill patients also make APRV conceptually attractive. As described earlier, spontaneous inspiratory efforts underlie the theoretic advantages of APRV. Because the spontaneous efforts are independent of the ventilator-triggered inflation/release phases, patients are permitted to breathe throughout the ventilator cycles, thereby improving patient-ventilator synchrony. Thus, APRV has the potential to lessen the need for deep sedation or analgesia and potentially eliminate the need for NMBA.

Disadvantages and Potential Limitations of APRV Use

APRV use in ALI has gained widespread acceptance in many intensive care units. However, several potential disadvantages and limitations of this ventilatory strategy in ALI should be noted. Importantly, the benefit of lung protective ventilation using the ARDSNet protocol has been well documented and validated in a multicenter study. APRV use, in spite of the conceptual advantages described earlier, has not systematically and consistently shown an improvement in clinically meaningful end points in human trials. Alveolar volutrauma is a function of the increased alveolar volume resulting from the alveolar distending pressure (P_{Alv}; or transpulmonary pressure, TPP). The latter is not routinely measured in mechanically ventilated patients with ALI. Clinically the plateau pressure (P_{Plat}) is often used as a surrogate for end-inspiratory stretch, but important caveats exist. Mathematically,

$$P_{Alv} \text{ or TPP} = \text{End inspiratory pressure } (P_{Plat} \text{ or } P_H) - \text{Pleural pressure} \qquad \text{(Equation 2)}$$

In APRV, the negative pleural pressures generated by spontaneous breathing are real, variable, and distributed heterogeneously throughout the lung. For instance, in APRV with a set P_H of 30 cm H_2O, a generated pleural pressure of (–)10 cm H_2O during a spontaneous patient effort would translate into a TPP of 40 cm H_2O, a level considered unsafe in clinical practice. By limiting sedation and use in APRV, this concern may be exacerbated by allowing greater

Clinical interest in APRV use has evolved from two basic premises: (1) APRV use as an alternative to standard modes of PC and VC for lung protective ventilation and (2) APRV use as a salvage therapy in ALI patients with refractory hypoxemia despite optimized settings on conventional mechanical ventilation. APRV may have several conceptual advantages in the ventilation of ALI patients (Box 74.E1). Despite chest radiographs often revealing homogeneous patterns of pulmonary infiltrates in ALI, the diseased lung is mechanically and histopathologically heterogeneous (Chapter 73). Regions of consolidated, atelectatic, aerated, and overinflated lung units not only exist next to one another, but their distribution throughout the lung varies considerably. In addition, gravitational forces typically contribute to dependent atelectasis across the sternovertebral axis in supine patients. Because of regional differences in lung mechanics in addition to regional differences in transpulmonary pressures, mechanically delivered tidal volumes are not uniformly distributed in ALI. Furthermore, patients with ALI often require deep sedation and sometimes pharmacologic paralysis, disrupting the normal contraction and movement of the diaphragm. When paralyzed and supine, the diaphragm is displaced in a manner such that the anterior portions of the lower lung zones receive preferential ventilation. Because perfusion continues to go preferentially to posterior segments (as a result of gravity), $\dot{V}_A/\dot{Q}$ mismatch increases. By preserving spontaneous breathing in these patients, the actively contracting diaphragm may minimize the sternovertebral gradient for atelectasis by augmenting regional ventilation to the most dependent portions of the injured lungs. Furthermore, by generating negative pleural pressures in the spontaneously breathing patient, this regional increase in transpulmonary pressures leads to improved $\dot{V}_A/\dot{Q}$ distribution and a reduced intrapulmonary shunt, particularly in the dependent portions of the injured lung. Therefore, central to the concept of APRV is the critical importance of preserving and encouraging spontaneous breathing by the patient throughout T_H.

The threshold opening pressure (TOP) refers to the airway tension that must be generated so that a gasless, collapsed alveolus will expand (*recruit*). The closing pressure, which is often less than the TOP for a given alveolus, refers to the tension that must remain in the alveolus to overcome its tendency to collapse when gas is emptied (*de-recruit*). The heterogeneous nature of ALI yields a wide spectrum of TOP for the diseased alveolar units. Optimal lung recruitment, therefore, is dependent not only on the absolute pressures delivered but also on the duration that this pressure is applied. Compared with VC utilizing high positive end-expiratory pressure (PEEP), APRV can achieve higher mean P_{aw} with similar or even lower end-inspiratory pressures. Additionally, the generated mean P_{aw} in APRV is more constant as there are fewer interruptions (e.g., ventilator cycles)—improving gas diffusion and augmenting collateral ventilation.

BOX 74.E1 ■ Potential Advantages and Disadvantages of APRV Use in ALI

Potential Advantages

- Improves alveolar recruitment
- Improves ventilation/perfusion distribution
- Minimizes ventilator-induced lung injury
- Limits sedative and neuromuscular blocking agent use

Disadvantages

- Lack of rigorous clinical trials documenting clinically meaningful end points
- May not consistently limit volutrauma and atelectrauma
- Lack of consensus guidelines on optimal settings
- Physician and staff inexperience can lead to errors of use
- Improvement in gas exchange may take hours (e.g., 6 to 18 hours) before maximal benefit is reached

APRV, airway pressure release ventilation; ALI, acute lung injury.

APRV and Human Clinical Studies

A number of clinical investigations in humans have been undertaken to test the hypothesis that APRV may be an advantageous ventilatory strategy in ALI. Although a detailed review of all these studies is beyond the scope of this chapter, several important findings and conclusions are worth mentioning. First, there have been very few randomized controlled trials (RCTs), and no trial design has had adequate methodology to evaluate the purported benefits of APRV versus the National Institutes of Health, National Heart, Lung and Blood Institute (NIH NHLBI) ARDS Clinical Trials Network (ARDSNet) low tidal volume (6 mL/kg predicted body weight [PBW]) ventilation strategy, which is considered the standard of care in the ventilatory management of ALI (Chapter 73, Table 73.3). Though investigators have shown improvements in physiologic end points such as oxygenation parameters, dead-space fraction, and degree of shunt using APRV compared to other modes of ventilation (PS, inverse ratio ventilation [PC-IRV], synchronized intermittent mandatory ventilation [SIMV], APRV without spontaneous breathing, etc.), these improvements do not necessarily translate into clinically meaningful end points.

TABLE 74.1 ■ **Initial Bi-Level and APRV Settings**

Parameter	Bi-Level	APRV
Pressure high (P_H)	≤ 30 cm H_2O	≤ 30 cm H_2O
Pressure low (P_L)	≥ 5 cm H_2O Often equals PEEP from prior mode	0 cm H_2O
Time high (T_H)	Variable; typically I:E = 1:1 to 2:1	4–6 seconds; I:E often > 8:1
Time low (T_L)	Variable; typically I:E = 1:1 to 2:1	0.5–0.8 seconds
Frequency	12–25 cycles/min	8–12 cycles/min
Pressure support	P_H: 0–1.5 cm H_2O (or ATC) P_L: ≥ 7 cm H_2O	P_H: 0–1.5 cm H_2O (or ATC) P_L: 0 cm H_2O

APRV, airway pressure release ventilation; PEEP, positive end-expiratory pressure; ATC, automatic tube compensation.

patient inspiratory effort and TPP swings. Furthermore, because APRV relies on a pressure mode of ventilation, V_T (during the release phase) is dependent on lung compliance, pressure levels, airways resistance, and release time. Changes in any of these parameters can adversely lead to large unintended changes in delivered tidal volume. As will be described in greater detail, one of the greatest challenges when using APRV is setting an optimal duration of T_L, which, in turn, depends on alveolar time constants (TCs). TC refers to the rate at which a lung unit empties (or fills) and is mathematically the product of airways resistance (R_{aw}) and static compliance (C_{St}). Therefore, the diseased lung units at greatest risk for atelectrauma (e.g., lowest C_{St}) will have the shortest TC and unfortunately are the first to de-recruit during the release phase. Furthermore, the rapid release phases could impart shearing forces to lung epithelial and endothelial structures not previously recognized in more conventional modes of ventilation.

Initial Application of APRV

Tables 74.1 and 74.2 summarize recommended initial settings for standard Bi-Level and APRV. These are only recommendations for initial settings and should be optimized based on individual patient physiology and lung mechanics and arterial blood gas (ABG) results.

SETTING PRESSURE HIGH (P_H)

The primary goal of P_H is to recruit atelectatic lung units and improve oxygenation without exposing the acutely injured lung to dangerous levels of pressure and tidal volume that may contribute to volutrauma. Given the heterogeneous nature of the lung insult and variable time constants within the lung, there is no exact pressure level at which recruitment stops and overdistention begins uniformly. Therefore, P_H is often limited to 30 cm H_2O based on extrapolation from ARDSNet guidelines that suggest keeping end inspiratory pressures ≤ 30 cm H_2O. If transitioning to APRV from conventional mechanical ventilation, P_H may be set at P_{Plat} (if on VC) or to IP + PEEP (if on PC). The P_H should be gradually reduced to keep release tidal volume (V_T) = ~6 to 8 mL/kg PBW while maintaining adequate oxygenation (PaO_2 ≥ 55 mm Hg).

SETTING PRESSURE LOW (P_L)

To maximize expiratory flow and optimize ventilation (e.g., remove CO_2), P_L should be set to 0 cm H_2O. Adding applied PEEP by setting P_L > 0 cm H_2O will, by definition, decrease V_T

Besides the aforementioned conceptual limitations of APRV use, several practical issues exist. Just as with any newly implemented technology, no clear consensus exists on optimal settings for APRV. In addition, available clinical guidelines on the monitoring and changing of settings based purely on lung mechanics and gas-exchange values are lacking.

Typically, the clinician will set FiO_2, P_H, P_L, T_H, and T_L. The frequency of releases (f) is not formally set because it is dependent on the set T_L and T_H (e.g., if T_H is 5.5 seconds and T_L is 0.5 seconds, then each respiratory cycle will be 6 seconds and f = 10 and I:E = 11:1). PS at T_H is commonly not applied as noted earlier. Alternatively, automatic tube compensation can be used at T_H instead of PS. The subtleties of choosing PS settings are more governed by ventilator manufacturers than clinicians (e.g., some ventilators only allow one PS setting in APRV or automatically set PS on T_H at 1.5 cm H_2O). After the initial implementation of APRV, 6 to 18 hours may be needed before the maximum benefit in oxygenation is achieved. The reason for this delay is not completely understood but may in part be a result of the role spontaneous breathing plays in improving $\dot{V}/\dot{Q}$ mismatch, decreasing shunt and the complex physiology of lung recruitment in ALI. Furthermore, lung recruitment may improve after hours on fixed APRV settings independent of P_{aw}. This may also be related to changes in regional iPEEP and the effect of lung hysteresis on alveolar recruitment in ALI.

TABLE 74.2 ■ **Initial APRV Settings in ALI**

Parameter	Initial Setting	Goal and Comments
Pressure high (P_H)	≤ 30 cm H_2O	Maximize recruitment and mean P_{aw}; target release V_T ~6–8 mL/kg PBW; conversion to APRV from VC/PC: $P_H = P_{Plat}$ (VC) or IP + PEEP (PC)
Pressure low (P_L)	0 cm H_2O	Minimize resistance to expiratory flow during release phase; short T_L will cause regional intrinsic PEEP
Time high (T_H)	4–6 seconds	Maximize recruitment and mean P_{aw}; may be incrementally increased in 0.5–1-second intervals to achieve goal oxygenation
Time low (T_L)	0.5–0.8 seconds	Maintain regional intrinsic PEEP; minimize spontaneous efforts; setting should balance de-recruitment with excess intrinsic PEEP/hypercapnia; see the text for setting based on expiratory flow
Frequency	8–12 cycles/min	Determined based on T_H and T_L settings
Pressure support (PS)	P_H: 0–1.5 cm H_2O P_L: 0 cm H_2O	Minimal PS is offered at P_H to prevent VILI; no support is offered at P_L as spontaneous efforts should not occur

APRV, airway pressure release ventilation; P_{aw}, airway pressure; V_T, release phase tidal volume; VC, volume assist control; PC, pressure assist control; P_{Plat}, plateau pressure; IP, inspiratory pressure; PEEP, positive end-expiratory pressure; VILI, ventilator-induced lung injury; PBW, predicted body weight (see Table 73.3, Chapter 73, for formulas to calculate PBW).

and potentially worsen respiratory acidosis, and may increase the patient's work of breathing. In concert with setting P_L at 0, T_L must be appropriately set in order to attain optimal iPEEP and prevent alveolar de-recruitment.

SETTING TIME HIGH (T_H)

T_H should initially be set at 4 to 6 seconds. Increasing durations of T_H directly impact mean P_{aw}, lung recruitment and may foster spontaneous breathing efforts by the patient. Decreasing durations of T_H may adversely impact mean P_{aw} and cause lung de-recruitment to such a degree that the benefit of APRV is lost. T_H may be extended beyond 6 seconds gradually (e.g., 0.5- to 1-second increments) to optimize PaO_2. Care should be taken as T_H is increased to prevent excessive iPEEP during the release phase.

SETTING TIME LOW (TL)

T_L is the single most important parameter to set in APRV. Unfortunately, determining the optimal T_L is often difficult and inexact. Nonetheless, setting T_L requires an understanding of respiratory time constants (TC) in ALI. Typically, it takes 4 to 5 TC (i.e., an exponential decline) for an alveolus to completely empty. Although T_L is abbreviated for APRV in an effort to maintain iPEEP, T_L should not be longer than 5 TC. Unfortunately, in ALI there is heterogeneity in alveolar TC and, of greater relevance, TC cannot be easily measured. However, even without an exact knowledge of actual TC values, appropriate T_L can be estimated based on the expiratory flow rate during the release phase (Figure 74.3). When the release phase begins (e.g., transition from P_H to P_L), expiratory flow is at its greatest, commonly referred to as the peak expiratory flow (PEF). This flow rate decays over the time and if the expiratory flow reaches 0 L/min during the release phase, then airway pressure has reached P_L (or 0 cm H_2O) and no iPEEP is present. Therefore, T_L should be

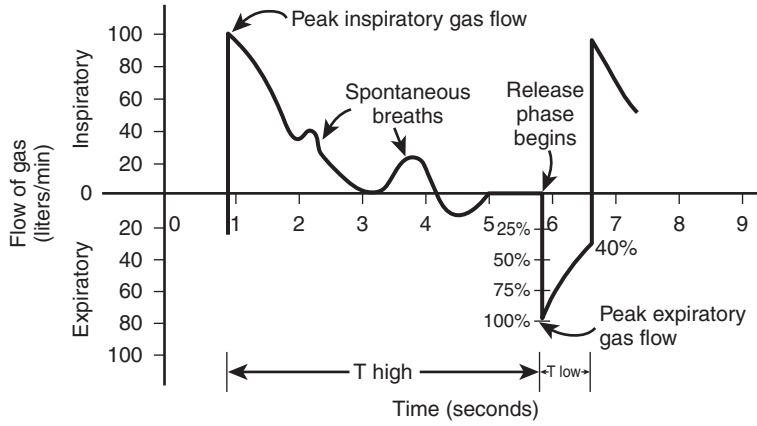


Figure 74.3 Flow-time graph of APRV. Release phase duration is set such that expiratory flow decays to 25% to 50% (e.g., 40%) of the peak expiratory flow before the ventilator cycles back to pressure high. This leads to intrinsic PEEP and prevention of alveolar de-recruitment. *(Adapted from Frawley PM, Habashi NM: Airway pressure release ventilation: theory and practice. AACN Clin Issues 12:234-246, 2001.)*

set such that the terminal expiratory flow rate, or the expiratory flow rate when the release phase ends (e.g., transition from P_L to P_H) is kept at 25% to 50% of the PEF. Important considerations are (1) T_L must be carefully monitored and adjusted frequently as the patient's lung mechanics change—it is not a "set and forget" parameter; (2) the worse the respiratory system compliance (C_{st}), the shorter T_L typically needs to be to prevent alveolar de-recruitment; (3) setting T_L too short can lead to progressive increases in iPEEP and can result in hemodynamic compromise; and (4) given the heterogeneity of the disease, T_L should be based on clinical scenario and evaluation of the patient-ventilator's flow-time graphs.

Potential Contraindications of APRV Use

Because APRV may not provide for adequate CO_2 elimination, allowance of spontaneous patient effort is often necessary. Therefore, several clinical scenarios exist where APRV use in ALI may not be appropriate. In ALI patients where there is a coexistent need for deep sedation (e.g., status epilepticus, increased intracranial pressure), APRV may not be able to provide enough ventilatory support and its potential benefits may be dampened if spontaneous patient efforts are limited. Similarly, care must be taken when using neuromuscular blocking drugs in patients on APRV. Extreme care should be taken when using APRV in patients with chronic obstructive pulmonary disease (COPD) or other obstructive airways disease (such as asthma). These patients often require prolonged expiratory times because of increased R_{aw}, and hemodynamic compromise may be unavoidable because of the progressive iPEEP accumulated during the brief release phases in APRV.

Adjusting APRV Parameters and Arterial Blood Gas Management

Arterial blood gas (ABG) monitoring can help to manage APRV, which can be complex. Many of the clinician set parameters (e.g., P_H, P_L, T_H, T_L) are interdependent, and changes in one may have profoundly negative effects on another parameter. Table 74.E1 lists a few representative ABGs and potential solutions.

TABLE 74.E1 ■ **Arterial Blood Gas (ABG) Management in APRV**

APRV Setting (P_H/P_L; T_H/T_L) Release V_T	ABG (pH/$PaCO_2$/PaO_2/HCO_3)	Potential Solution(s)
P: 25/0; T: 4/0.6 f = 13; FiO_2: 1; V_T 6 mL/kg PBW	7.36/48/51/25	Increase P_H up to 30 to increase mean P_{aw} Lengthen T_H by 0.5–1 keeping T_L at 0.6 This will decrease f to ~11 but may not affect $PaCO_2$ given increase in release V_T from increased recruitment and driving gradient during release phase Ensure new V_T are not excessive
P: 30/0; T: 5/0.6 f = 11; FiO_2: 0.8; V_T 6 mL/kg PBW	7.22/79/73/27	Accept permissive hypercapnia Assess spontaneous efforts and sedation Assess flow-time waveform to see if T_L can be extended to 0.7–0.9
P: 25/0; T: 5.4/0.5 f = 10; FiO_2: 1; V_T 6 mL/kg PBW	7.16/69/50/24	Increase P_H up to 30; this will have a dual effect of improving $PaCO_2$ and PaO_2 Assess appropriateness of T_L duration if EF terminates > v50% of PEF, lengthen T_L; if EF terminates < 25% of PEF, shorten T_L Consider increasing T_H in small increments and keeping T_L fixed if EF is 25%–50% of PEF Ensure new V_T are not excessive
P: 30/0; T: 6/0.8 f = 9; FiO_2: 0.6; V_T 8 mL/kg PBW	7.34/50/94/25	Adjust to decrease release V_T to prevent VILI; many potential options: decrease P_H, decrease T_H, decrease T_L based on flow-time graph Ensure $PaCO_2$ and pH are acceptable under new settings

APRV, airway pressure release ventilation; P_H, pressure high; P_L, pressure low; T_H, time high; T_L, time low; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; HCO_3, serum bicarbonate concentration; P, pressure; T, time; f, release frequency per minute; FiO_2, fraction of inspired oxygen; V_T, release phase tidal volume; P_{aw}, airway pressure; s, seconds; EF, expiratory flow; PEF, peak expiratory flow; VILI, ventilator-induced lung injury.

HYPOXEMIA

The major ventilatory determinants of PaO_2 are P_H, T_H, T_L, and FiO_2. Modest increases in the magnitude or duration of the inflation phase can have profound effects on lung recruitment. An inappropriately set T_L can cause hypoxemia by allowing excessive alveolar de-recruitment during release phases. However, if T_L is set too short leading to an incremental progressive increase in iPEEP, hemodynamic deterioration can independently worsen hypoxemia. Finally, a high frequency of release phases per minute can indirectly lead to hypoxemia by discouraging spontaneous breathing and negatively impacting lung recruitment by impairing collateral ventilation.

HYPERCAPNIA

As discussed earlier, APRV often relies on spontaneous respiratory efforts to augment the elimination of CO_2. Use of sedatives should be avoided if possible and, if necessary, should be based on an objective sedation scale in order to minimize total dose required (Chapter 5).

Liberation from APRV

Liberating from APRV has not been standardized. If the insult that required the need for APRV is resolving (e.g., ALI) and oxygenation is improving, potential options for weaning include (1) resumption of standard ventilation to volume control or (2) weaning of APRV parameters. Sometimes transition to volume control may lead to profound alveolar de-recruitment despite adequately applied PEEP and may necessitate prompt return to APRV. In such cases, weaning from APRV involves steadily decreasing P_H and prolonging T_H. This will gradually decrease mean P_{aw}. Initially T_L should be kept constant with the increases in T_H so that release cycle frequency decreases. Although there is no consensus on how quickly this should be done, small changes can typically be made every 2 to 4 hours with frequent reassessments (e.g., decrease P_H in 2 to 4 mm Hg increments and increase T_H by 0.5- to 1-second increments). There should be a gradual increase in spontaneous efforts to offset the decreased ventilatory support delivered by the ventilator. When release cycles are < 4/minute and the majority of ventilation is supported by spontaneous efforts on P_H 12 to 16 mm Hg, a spontaneous breathing trial can be considered.

An annotated bibliography can be found at www.expertconsult.com.

Neuromuscular blocking agents should be completely avoided and, if necessary, should prompt the provider to search for an alternative mode of ventilation. T_L should be assessed by evaluating the flow-time waveform to confirm that the expiratory flow terminates at 25% to 50% of the peak expiratory flow. If T_L is set appropriately, further extension of T_L (e.g., to < 25% of PEF) in an effort to increase release, V_T may lead to a paradoxical worsening of acidosis because of profound alveolar de-recruitment and loss of gas-exchange surface area within the lung. Increases in P_H and T_H can improve alveolar ventilation by increasing mean P_{aw} and recruitment. Increasing P_H will also improve the driving gradient between P_H-P_L and potentially increase the release V_T. Commonly, the frequency of releases may be increased to improve hypercapnia—however, caution should be noted with a frequency > 12/minute as this may negatively impact mean P_{aw} and paradoxically worsen lung recruitment. Permissive hypercapnia (pH > 7.2) should be considered and is frequently well tolerated in most patients with ALI.

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This is a retrospective study comparing APRV to PSV in patients with acute lung injury.

CHAPTER 75

Acute Respiratory Failure Due to Asthma

Audreesh Banerjee ■ Reynold A. Panettieri Jr.

Severe asthma exacerbations (or "attacks") can progress to respiratory failure that requires admission to the intensive care unit (ICU). Rapid diagnosis of impending respiratory failure and appropriate initiation and management of mechanical ventilation are essential (Chapters 1 and 2). Many features of severe asthma parallel severe exacerbations of chronic obstructive pulmonary disease (COPD; see Chapter 76).

Pathophysiology

Asthma is characterized by airway inflammation, reversible airflow obstruction, and airway hyperresponsiveness. Multiple factors can trigger asthma exacerbations, such as allergens, cold air, exercise, and emotional stress; exacerbations may be progressive or abrupt in onset. Airway inflammation is characterized by bronchial wall inflammation, edema, and tenacious secretions or mucus plugs. Over time, chronic stimulation and inflammation of the airways engender airway remodeling that compromises airway reversibility, a traditional hallmark of asthma. Likewise, rapid reversibility may not be apparent during acute asthma attacks.

Acute Asthma Exacerbations

CLINICAL SIGNS AND SYMPTOMS

Patients with severe acute asthma exacerbations typically present with dyspnea, wheezing, and cough. Other causes in the differential diagnosis of these symptoms include "cardiac asthma" (secondary to left-sided congestive heart failure), upper airway obstruction, pneumonia, "laryngeal asthma" (vocal cord dysfunction syndrome), anaphylaxis, and an acute exacerbation of COPD. Because some of these entities may have a component of airway hyperreactivity, differentiating among these diseases solely on the basis of bronchodilator responsiveness is difficult and may be misleading.

A rapid yet complete clinical assessment of the patient in respiratory distress is necessary for accurate diagnosis. Therapy, however, must begin simultaneously with diagnostic assessment. Clinical indicators of severe airflow obstruction include breathlessness at rest, an inability to speak full sentences, tachycardia, orthopnea, diaphoresis, pulsus paradoxus greater than 10 mm Hg, impaired mental status (a sign of carbon dioxide narcosis, hypoxemia, or both), central cyanosis, marked accessory muscle use, and evidence of diaphragmatic fatigue such as paradoxical breathing (inward instead of outward movement of the abdominal wall during inspiration while supine). Auscultatory findings may be misleading because wheezing alone does not accurately predict the severity

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of airway obstruction. In some patients, significant wheezing resolves after bronchodilator therapy. Conversely, diminished or lack of wheezing (a "quiet" chest) may ominously signal worsening air movement in the setting of progressive airway obstruction. Distant breath sounds with no wheezing may occur in patients with severe but stable airway obstruction. Knowing a patient's baseline clinical pulmonary function testing results is helpful in assessing the patient's degree of acuity.

Stridor denotes upper airway obstruction, with a differential diagnosis that includes acute epiglottitis, laryngeal asthma (paradoxical vocal cord dysfunction syndrome), laryngeal edema from anaphylaxis or angioedema, a foreign body, or malignancy. Laryngeal asthma is a clinical diagnosis, sometimes confirmed by observing paradoxical closure of the vocal cords during respiration, especially during inspiration when the vocal cords are normally fully abducted. Such patients can mimic life-threatening asthma exacerbations, and many have coexistent asthma, making their evaluation particularly challenging.

Distinguishing a severe asthma flare from an acute exacerbation of COPD can also be difficult. Often, prior history of tobacco use, chronic daily sputum production, irreversible airway obstruction, resting blood gas abnormalities, or radiologic evidence of emphysema point to the COPD.

OBJECTIVE MEASURES OF AIRFLOW OBSTRUCTION

In addition to clinical assessments, a peak expiratory flow rate (PEFR), the forced expiratory volume in 1 second (FEV_1), or both should be measured in all patients with asthma who can tolerate such measurements. These measurements can be safely performed in many patients, typically at presentation and 15 to 20 minutes after bronchodilator therapy; however, one should defer such measurements if severe airway obstruction or overt respiratory failure is clinically obvious, as these maneuvers can precipitate cardiopulmonary arrest in severe asthmatic patients. Although a PEFR < 150 L/minute or an FEV_1 < 1 L confirms severe obstruction, comparison to baseline pulmonary function measurements (if available) is even more helpful. A PEFR 33% to 50% of predicted indicates a severe asthma exacerbation, whereas PEFR < 25% predicted before treatment or < 40% predicted after treatment suggests a life-threatening exacerbation and identifies patients requiring hospitalization and admission to an ICU.

HYPOXEMIA

Hypoxemia in an acute asthma exacerbation is partly due to airway narrowing that prompts mismatching of ventilation and perfusion. Mucus plugging creates shunts through nonventilated alveoli. One should obtain an arterial blood gas (ABG) analysis in addition to monitoring by continuous pulse oximetry in severe airflow obstruction. ABG findings during an acute asthma attack can include an acute respiratory alkalosis with hypocapnia associated with mild to moderate hypoxemia (Table 1.2 [Chapter 1] and Table 75.1). With severe airflow obstruction, a normal or slightly elevated $Paco_2$ may reflect impending respiratory failure and necessitate close observation and aggressive treatment. In COPD, unlike asthma, patients often manifest an abnormal baseline ABG and presentation with respiratory failure reveals worsened hypercapnia (see Table 75.1 and Chapter 1, Table 1.2). Chest radiographs generally have limited usefulness in the evaluation of patients with asthma unless there is concern for pneumonia or pneumothorax.

Medical Management of Patients with Severe Asthma

OVERVIEW

The management is similar in both severe acute asthma and COPD exacerbations (see Box 75.1 and Chapter 76). Therapies include treating reversible bronchospasm and airway inflammation,

TABLE 75.1 ■ **Interpretation of Carbon Dioxide Retention in Arterial Blood Gas Analysis**

Acute respiratory acidosis	For every 10 mm Hg increase in $Paco_2$, bicarbonate will increase by 1 mEq/L (±0.3 mEq/L)* and pH will decrease by 0.08 units
Chronic respiratory acidosis	For every 10 mm Hg increase in $Paco_2$, bicarbonate will increase by 0.4 mEq/L (±0.4 mEq/L)* and pH will decrease by 0.03 units

*95% confidence intervals.

BOX 75.1 ■ Initial Management of Severe Bronchospasm

Timing

- Therapy must be initiated before completion of the physical examination and data collection

Beta-Agonist Therapy

- Albuterol 2.5–5 mg diluted in 3 mL saline administered via nebulizer
- Nebulized treatments should be administered every 20 minutes
- Maximal benefit is usually seen after three treatments

Steroid Therapy

- Corticosteroid therapy is begun simultaneously with bronchodilator therapy
- Methylprednisolone 125 mg IV × one dose followed by 0.5–1 mg/kg IV q6h

Oxygen Therapy*

- Correct hypoxemia (keep Sao_2 > 92%) by administering supplemental oxygen
- Use nasal prongs for asthma patient

Assisted Ventilation

If there is worsening hypercapnia, respiratory acidosis, hypoxemia, or signs of respiratory muscle fatigue (e.g., respiratory paradox; see text):

- Attempt non-invasive ventilation using a full face mask (Chapter 3) in patients who are awake, alert, and hemodynamically stable
- Otherwise, proceed with endotracheal intubation (via oral route) and mechanical ventilation

**Patients with chronic obstructive pulmonary disease (COPD) who are at risk for carbon dioxide retention require "controlled" oxygen therapy and serial arterial blood gas determinations to monitor $Paco_2$ levels.*

IV, intravenously; q6h, every 6 hours.

correcting hypoxemia and respiratory acidosis, managing secretions, removing or treating precipitating factors, and avoiding iatrogenic complications (such as barotrauma and hemodynamic instability). But because of differences in the underlying pathophysiologic mechanisms, therapeutic approaches differ somewhat for each disorder.

BRONCHODILATORS

Repetitive or continuous administration of short acting β_2-selective adrenergic agonists is a cornerstone of therapy for acute, severe airway obstruction from both asthma and COPD. Administer albuterol by nebulization because patients in acute respiratory distress often struggle to coordinate inspiration with use of metered dose inhalers (MDIs). Parenteral dosing of

beta-agonists in adult patients offers no therapeutic advantage and has frequent and serious toxic side effects. Note that similar toxicities (tachycardia, palpitations, nausea, vomiting, hypokalemia, lactic acidosis, and myocardial ischemia) can occur with high doses of inhaled albuterol (> 10 to 15 mg/hour). One should consider subcutaneous administration of epinephrine or terbutaline in patients unresponsive to continuous nebulized β_2 agonists, or unable to tolerate inhaled therapy. In hospitalized, *non-ICU* patients, MDIs provide equivalent efficacy to nebulizer therapy, at much lower cost.

Anticholinergic agents (e.g., ipratropium bromide) block airway muscarinic receptors, causing bronchial smooth muscle relaxation and decreased submucosal gland secretions. The combination of β_2 agonists and anticholinergic therapy improves PEFR and FEV_1 when compared to β_2 agonists alone. In addition, inhaled ipratropium has improved bronchodilation in patients with acute bronchospasm induced by beta-blockers and monoamine oxidase inhibitors.

Methylxanthines (e.g., theophylline) play a limited role in the modern management of acute airway obstruction. Their mechanism of action remains unclear, and multiple studies demonstrate no additional beneficial effect of methylxanthines over standard β_2-agonist and corticosteroid therapy. However, one should maintain methylxanthines in the acute setting for patients who take them chronically, as adjuncts for refractory severe bronchospasm. Methylxanthines require careful dosing (Table 75.E1), with closely monitored levels maintained between 8 and 10 mg/dL. One should observe patients closely for toxicities, which include nausea, vomiting, cardiac arrhythmias, and seizures.

OXYGEN THERAPY

Hypoxemia in acute asthma exacerbations can usually be corrected with low-flow oxygen administered via nasal cannula, to maintain oxygen saturations above 90% in most patients. Pregnant patients and patients with underlying heart disease should be maintained with oxygen saturations above 95%.

ANTIBIOTICS

Few data implicate a role for bacteria in inciting an acute asthma exacerbation. However, asthma exacerbations associated with acute respiratory failure frequently warrant empiric antibiotics, covering for common, community-acquired organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.

OTHER PHARMACOLOGIC INTERVENTIONS

Although few data support its efficacy, maintaining adequate hydration is often recommended to decrease the viscosity of airway secretions and prevent bronchial mucous plugging. Chest physical therapy with postural drainage can aid mobilization of thick secretions, thereby decreasing mucus plugging and improving oxygenation. Aerosolized *N*-acetylcysteine, a mucolytic agent, is ineffective in managing persistent airway secretions and may actually precipitate further bronchospasm.

Little evidence supports the use of magnesium sulfate for the treatment of acute bronchospasm. However, magnesium (2 g IV over 20 minutes) can be an adjunctive therapy to corticosteroids and beta agonists in life-threatening asthma, or exacerbations that remain severe after 1 hour of intensive therapy.

Leukotrienes are inflammatory mediators implicated in asthma, and leukotriene receptor antagonists demonstrate some efficacy in outpatient management of asthma. Few, limited clinical trials suggest any benefit of these agents in an acute, severe asthma exacerbation.

TABLE 75.E1 ■ **Theophylline Dosing in Adults with Acute Bronchospasm**

DOSING	INTRAVENOUS AMINOPHYLLINE*
Loading Dose (over 20 minutes)†	5 mg/kg predicted body weight‡ (PBW)
History of theophylline use:	
—None	
—Oral theophylline use	0–3 mg/kg PBW
Maintenance Dose§	
Patient category:	
—Nonsmoker	0.6 mg/kg PBW/h
—Smoker	0.3 mg PBW/kg/h
—Critically ill	0.6 mg PBW/kg/h
—Congestive heart failure	0.2 mg PBW/kg/h
—Severe pneumonia	0.2 mg PBW/kg/h

*Dosing expressed in *aminophylline* equivalents (theophylline dose = 0.8 × aminophylline dose).
†If possible, serum theophylline levels should be obtained before administration, especially if there is a history of theophylline use.
‡Predicted body weight (PBW) for adults can be estimated from formulas in footnotes of Table 17.1 or Table 73.2 or from Appendix F's Tables of PBW according to height of women and men.
§Theophylline levels should be measured 12 to 24 hours after loading and more frequently if symptoms or signs of theophylline toxicity are evident. Target level = 8 to 10 μg/mL. A 1-mg/kg PBW aminophylline dose will increase the serum concentration by approximately 2 μg/mL.
From Dellinger RP: Life-threatening asthma. In Parillo JE, Dellinger RP (eds): Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 2nd ed. St Louis: Mosby, 2001, p 729.

CORTICOSTEROIDS

Corticosteroids decrease acute airway inflammation, increase the efficacy of β adrenergic receptor activation, and inhibit the migration and function of inflammatory cells, with an onset of action between 2 and 6 hours. Therefore, administer corticosteroids as quickly as possible in patients undergoing acute severe airway obstruction. No advantages exist to high doses (methylprednisolone 1.5 to 2 mg/kg every 6 hours) over lower doses (methylprednisolone 0.5 to 1 mg/kg every 6 hours), or the parenteral over oral route. In the severely dyspneic patient, however, intravenous (IV) administration is preferred. A methylprednisolone load of 125 mg IV, followed by 0.5 to 1 mg/kg IV every 6 hours, is one recommended initial treatment. Also, although controversial, repetitive administration of high-dose inhaled corticosteroids may provide additional benefit in addition to systemic corticosteroid therapy. Upon clinical improvement, one should convert parenteral to an oral steroid (e.g., prednisone) tapered over a minimum of 2 to 3 weeks.

Mechanical Ventilation of Patients with Severe Asthma

Patients with asthma who present with signs of impending cardiac or respiratory arrest should be emergently intubated and mechanically ventilated. However, many patients with a severe asthma exacerbation and acute respiratory acidosis respond to aggressive medical therapy and avert mechanical ventilation. Patients demonstrating clinical deterioration despite aggressive therapy, as evidenced by hemodynamic instability, altered mental status, exhaustion, worsening hypercapnia, acidosis (pH < 7.25), or progressive hypoxemia on serial ABG determinations, should be intubated and mechanically ventilated. Some trials suggest improved outcomes in patients undergoing asthma exacerbations with non-invasive ventilation (Chapter 3), but the evidence remains inconclusive and less strong than its use in COPD flares.

Generally, orotracheal intubation with a large endotracheal tube (≥ 8 mm) is preferred, to facilitate suctioning, minimize airflow resistance, and possibly reduces the risk of sinusitis. Patients with asthma often have nasal polyps, also favoring intubation orally.

DYNAMIC HYPERINFLATION

Dynamic hyperinflation (DHI) complicates ventilatory management of patients with severe obstructive airway disease. The severe airways obstruction leads to prolonged expiratory time. In DHI, the lungs fail to empty completely before the next inspiration, causing increases in end expiratory lung volume, a phenomenon known as "breath stacking." When end expiratory lung volume exceeds baseline functional residual capacity (FRC), patients experience DHI of the lung because of the trapped gas. This results in intrinsic positive end expiratory pressure ($PEEP_i$, or auto-PEEP) caused by the recoil pressure of the lungs and chest wall above FRC (see Figures 2.3 and 2.6 in Chapter 2).

A rise in plateau pressures can indicate DHI in ventilated patients, as patients with severe airway obstruction generally experience elevations in peak (from increased airway resistance during inspiration) but not plateau pressures. $PEEP_i$ can be demonstrated at the bedside by occluding the expiratory port of the ventilator for 1 to 3 seconds if timed just before the *end of* expiration and observing a rise in airway pressure (see Figure 2.6 in Chapter 2). In most modern ventilators, a built-in shutter valve at end expiration serves the same purpose. In patients who are not paralyzed, measurement of $PEEP_i$ is less reliable because of error introduced by patient efforts. Therefore, this assessment should be considered a rough estimate in nonparalyzed patients. On ventilators with a "flow versus time" display, simply observing expiratory flow at the onset of inspiration indicates the presence of DHI (see Figure 2.7 in Chapter 2).

DHI has multiple adverse effects. Gas trapping overdistends some lung regions and compresses adjacent lung regions, resulting in hypoxemia if the compressed regions have lower $\dot{V}/\dot{Q}$ than the distended regions. The discomfort from DHI can lead to patient/ventilator asynchrony, increasing CO_2 production, airway pressures, and hypercapnia (Chapter 47). DHI also increases the negative intrathoracic pressure generated by the patient that is necessary to trigger a ventilator breath, increasing the inspiratory work of breathing and contributing to tachypnea, agitation, ineffective inspiratory efforts, and patient/ventilator asynchrony. Increased positive intrathoracic and pleural pressures can decrease venous return to the heart, diminishing cardiac output while inducing systemic hypotension, especially in patients with decreased intravascular volume. One can easily diagnose hypotension caused by $PEEP_i$ by rapidly disconnecting the patient from the ventilator and giving three to four breaths per minute by means of a manual resuscitation bag. This maneuver allows sufficient expiratory time for the overinflated lungs to decompress. Importantly, in addition to DHI, patients with acute respiratory failure have multiple possible etiologies of hypotension, including sedation, sepsis, poor fluid intake, and use of intubating and paralytic agents.

The development of DHI also increases the risk for barotrauma. End-inspiratory lung volume more than 20 mL/kg greater than FRC is associated with a higher risk of barotrauma as well as hypotension. High airway resistance in severe obstructive airway disease increases peak airway pressures and induces a large gradient between peak and alveolar pressures. Because studies suggest that the plateau rather than the peak pressure increases the risk of barotrauma, current recommendations are to maintain plateau pressures at less than 30 cm H_2O.

Although DHI and hence $PEEP_i$ are universally present in any mechanically ventilated patient with severe airway obstruction, their presence may or may not cause overt clinical problems. The first strategy to reduce DHI is to treat the underlying condition. Additionally, one can decrease $PEEP_i$ by employing a variety of maneuvers designed to increase expiratory time and lower the patient's mean intrathoracic pressure (Chapter 2). These include decreasing the respiratory rate or increasing the inspiratory flow rate, thereby decreasing inspiratory time and changing the inspiratory to expiratory (I:E) ratio. Generally, a high inspiratory flow rate is used for patients with acute severe airflow obstruction, so decreasing minute ventilation ($\dot{V}_E$) will be more effective in decreasing plateau pressures and DHI. The technique of increasing extrinsic PEEP to improve triggering and decrease air trapping in patients with $PEEP_i$ with acute asthma flares remains controversial.

Patients demonstrating severe DHI, manifested by refractory hypoxemia or hemodynamic compromise, may benefit from an "air dumping" maneuver, sufficiently lowering the respiratory rate to let trapped air escape for short time periods during mechanical ventilation. This usually necessitates heavy sedation of the patients. A decrease in plateau pressures (in volume-cycled ventilation) or an increase in tidal volumes (in pressure-cycled ventilations) indicates a successful air dumping maneuver. If plateau pressures continue to rise (> 30 cm H_2O), one should manage the patient by controlled hypoventilation and permissive hypercapnia. A moderate respiratory acidosis occurs but is usually well tolerated. If arterial pH falls to less than 7.20 to 7.25, however, some clinicians recommend treating with a bicarbonate infusion rather than increasing $\dot{V}_E$. Others do neither but continue close monitoring for adverse effects of the acidosis.

To control $\dot{V}_E$ resulting in permissive hypercapnia requires that the patient not "trigger" the ventilator. This can be accomplished in most patients by heavy sedation alone using a continuous infusion of benzodiazepines (such as lorazepam) or propofol (Chapter 5). In some cases, complete pharmacologic muscle paralysis may be necessary to suppress inspiratory efforts and decrease DHI. One should use neuromuscular blocking agents only with extreme caution and for a minimal duration. The combination of high-dose corticosteroids and a neuromuscular blocking agent administered for more than 24 hours is associated with an increased risk of a debilitating myopathy and prolonged weakness (Chapters 6 and 48).

Extraordinary measures are described and an annotated bibliography can be found at www.expertconsult.com.

EXTRAORDINARY THERAPIES

Unconventional therapies have been attempted in mechanically ventilated patients with severe airflow obstruction who deteriorate despite all conventional treatments. These methods include bronchoscopy to remove mucus plugs, general anesthesia to reduce airway resistance from bronchospasm, respiration with a low-density helium-oxygen (Heliox) mixture to lower the frictional resistance of turbulent gas flow, and partial cardiopulmonary bypass with extracorporeal membrane oxygenation and carbon dioxide removal (Chapter 88). Although Heliox potentially decreases airway resistance and improves deposition of nebulized medications, current studies show no clear benefits except perhaps in patients with the most severe asthma exacerbation. If using Heliox, note that nebulizer flow rates, peak flow, and pulmonary function measurements should all be adjusted. Although case reports and a retrospective cohort study suggest extracorporeal carbon dioxide removal may prove beneficial in patients with refractory status asthmaticus, complications are common with this therapy, and currently no clear guidelines describe when a patient with a severe asthma exacerbation would benefit from extracorporeal support. Nonetheless, patients with a severe asthma exacerbation who continue to show evidence of airway obstruction, hypercapnia, and dynamic hyperinflation on maximal medical therapy and mechanical ventilation should be evaluated by both the ICU physician and the cardiothoracic surgeon to consider whether the patient may benefit from such intervention.

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CHAPTER 76

Acute Respiratory Failure Due to Chronic Obstructive Pulmonary Disease

Michael W. Sims

Acute respiratory failure resulting from severe exacerbation of chronic obstructive pulmonary disease (COPD) is commonly encountered in the intensive care unit (ICU) and is a major source of morbidity and mortality from COPD. Acute exacerbation of COPD (AECOPD) is defined as a sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variations that is acute in onset and may warrant additional treatment in a patient with underlying COPD. The cardinal symptoms of AECOPD are increased dyspnea, increased cough and sputum volume, or increased sputum purulence. In the ICU setting, AECOPD typically involves severe dyspnea, gas exchange abnormalities with or without respiratory acidosis, and the potential need for mechanical ventilatory support (see Box 76.1 for indications for ICU admission). As most cases of AECOPD are caused by reversible factors, attentive management can result in favorable outcomes.

Etiology and Pathophysiology

The most common cause of AECOPD is respiratory infection, with an estimated 50% of cases caused by bacterial infection of the lower respiratory tract. The most commonly isolated organisms are *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*, with *Pseudomonas aeruginosa* (and possibly Enterobacteriaceae such as *Escherichia coli* and *Klebsiella pneumoniae*) playing a role in more advanced disease. Knowledge of these commonly isolated organisms guides empiric antibiotic choices for treatment of AECOPD (discussed further later in the chapter).

Respiratory viral infection also plays a major role in AECOPD and may portend a slower recovery than with bacterial infection. Rhinovirus is the most commonly isolated viral pathogen, but influenza, parainfluenza, respiratory syncytial virus, coronavirus, and adenovirus may also precipitate AECOPD, depending on the season of year.

Noninfectious agents contributing to AECOPD may include sedative overdose, aeroallergens, and air pollutants, such as sulfur dioxide, nitrogen dioxide, particulate matter, and ozone. Lastly, comorbid conditions such as congestive heart failure and pulmonary embolism may mimic AECOPD or may directly induce acute respiratory failure by raising ventilatory demands above the level that can be sustained by a patient with underlying COPD (Chapter 1, Figures 1.2 and 1.5, and Appendix B, Figure B2).

AECOPD is an acute inflammatory event, marked by increased numbers of neutrophils, macrophages, and, in the case of viral infection, eosinophils in the sputum. Defects in innate immunity may predispose patients with COPD to infections, which then induce acute

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BOX 76.1 ■ Indications for ICU Admission for Patients with Acute Exacerbation of COPD

- Severe, persistent dyspnea requiring more frequent administration of bronchodilators than can be accommodated outside of the ICU setting
- Changes in mental status (confusion, lethargy, coma)
- Severe or worsening hypoxemia, hypercapnia, or respiratory acidosis despite initial therapy
- Need for mechanical ventilatory support*
- Hemodynamic instability

**Note that in selected centers, non-invasive ventilation can be safely delivered outside of the ICU setting, provided adequate staffing, training, and experience of nurses and respiratory therapists. In general, however, ICU admission is recommended for patients requiring non-invasive ventilation.*

Modified from Rabe KF, Hurd S, Anzueto A, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 176:532-555, 2007.

airway inflammation. This inflammation increases mucus secretion, airway edema, and airway hyperresponsiveness, thereby narrowing airway luminal diameter and producing the airflow obstruction, dynamic hyperinflation, and ventilation-perfusion mismatch that characterize AECOPD. Increased serum levels of fibrinogen, C-reactive protein, and inflammatory cytokines and chemokines during AECOPD suggest that these episodes may also have systemic manifestations.

Respiratory failure in AECOPD may be multifactorial, with infection and inflammation superimposed upon the loss of alveolar volume (caused by emphysema) and impaired respiratory mechanics (e.g., flattened or inverted diaphragms) characteristic of COPD (in contrast to asthma; see Chapter 75). Infection and inflammation may evoke additional reductions in elastic recoil, further impairing ventilation and oxygenation that is generally compromised even at baseline. Elevated residual volume in patients with COPD compromises inspiratory capacity and breathing reserve. As a consequence, patients compensate for hypoxemia with tachypnea, which promotes air trapping by decreasing expiratory time, further increasing the work of breathing, leading to respiratory muscle fatigue and eventually respiratory failure.

Clinical Evaluation

Because patients admitted to the ICU with a severe AECOPD are at high risk for rapid clinical deterioration, it is important to focus the initial evaluation so as not to delay the initiation of life-saving therapies. A brief, directed medical history should elucidate any significant comorbid illnesses; onset, duration, and severity of any factors indicating an etiology for the AECOPD (e.g., sick contacts with flulike or respiratory illnesses, fever, cough, sputum volume, and purulence); and any features suggesting a possible alternative diagnosis (e.g., chest pain, orthopnea, ankle swelling, calf pain). Initial examination should focus primarily on the cardiopulmonary system, with attention to discovering and rapidly acting on hypoxemia, hemodynamic instability, lethargy or confusion, or signs of an unsustainable pattern of breathing (e.g., rapid shallow breathing > 40 breaths/min, extensive use of accessory muscles, or paradoxical movement of the chest and abdomen). After treating any immediate life-threatening complications, a more comprehensive history and physical examination can then be performed.

Routine laboratory studies, an arterial blood gas (ABG), and an electrocardiogram should be obtained, as well as a chest radiograph and a sputum culture with antibiotic sensitivities if the patient can produce a sample. Although predictive of outcomes during AECOPD, spirometry

is generally impractical in the ICU, where respiratory distress and frequent coughing typically prevent valid and reproducible maneuvers.

Interpretation of the ABG in a patient with COPD can be challenging because some patients have abnormal blood gases at baseline. Typical *baseline* abnormalities in a patient with severe COPD are mild to moderate hypoxemia and variable degrees of chronic respiratory acidosis. The latter is well compensated by renal bicarbonate retention, so that the pH may be near normal despite significant hypercapnia. It is helpful to compare the results of an ABG determination during an AECOPD with those obtained when the patient was in a stable baseline condition, if available. However, a simple rule of thumb can help differentiate acute from chronic respiratory acidosis (see Table 75.1 and Chapter 1, Table 1.2). The presence of acute respiratory acidosis, particularly with a pH < 7.30, is concerning and suggests the need for mechanical ventilatory support (discussed further later in the chapter).

Medical Management

The goals of therapy for severe AECOPD include improving airflow and relieving symptoms of bronchospasm, reducing acute airway inflammation, correcting hypoxemia and acute respiratory acidosis (but not overcorrecting the pH; see Appendix B), managing respiratory secretions, identifying and treating precipitating factors, and avoiding iatrogenic complications such as nosocomial infection or venous thromboembolism. To achieve these many goals, a multimodality approach is generally used that involves medications (see Table 76.1), controlled oxygen administration, nutritional supplementation, respiratory and physical therapy, and mechanical ventilatory support.

BRONCHODILATORS

Inhaled short-acting beta-agonists (e.g., albuterol) ameliorate bronchospasm, provide rapid symptomatic relief, and are the mainstay of initial therapy (see Box 76.1). Albuterol may be administered as 2.5 mg/3 mL saline via nebulizer or 2 to 4 puffs via metered dose inhaler (MDI) with a spacer. In the setting of severe AECOPD in the ICU, albuterol is generally given every 1 to 4 hours as needed, initially, with less frequent dosing as the patient improves. Higher doses (e.g., 5 mg nebulized) and continuous nebulizer treatments have not been proven more effective and are not recommended for routine use. Although albuterol delivered by MDI with a spacer is as efficacious as nebulized albuterol in hospitalized patients *outside* of the ICU, nebulization is generally preferred in nonventilated ICU patients because severe respiratory distress may interfere with proper MDI technique. In contrast, mechanically ventilated patients are typically administered albuterol by MDI through the ventilator circuit, which acts as a spacer. Side effects of albuterol include tremor, tachycardia, nausea, palpitations, nervousness, insomnia, and mild hypertension. Rarely, particularly with very high doses of inhaled albuterol (10 to 15 mg/hour), patients may experience lactic acidosis, seizures, tachyarrhythmias, and hypokalemia. Paradoxical bronchoconstriction is extremely rare but has been reported.

Inhaled short-acting muscarinic antagonists (e.g., ipratropium bromide) relieve bronchospasm and may decrease airway secretions. Ipratropium can be administered as 500 μg/2.5 mL saline via nebulizer or 2 puffs via MDI with a spacer. Dosing frequency is typically every 4 hours as needed, with less frequent dosing as the patient improves. Similar to albuterol, nebulizer administration is generally preferred for the nonventilated ICU patient and MDI administration for the mechanically ventilated patient. Although ipratropium in combination with albuterol improves bronchodilation over albuterol alone in stable COPD, this finding has not been reproducibly observed in the setting of AECOPD. Nonetheless, ipratropium is typically used with albuterol, and the combination offers the theoretic advantages of employing complementary mechanisms of action and merging the fast onset of albuterol with the more sustained activity of ipratropium.

TABLE 76.1 ■ **Pharmacologic Management of Severe Acute Exacerbation of COPD in the ICU setting**

Drug Class/Drug	Dosing Regimen	Notes
Short-Acting Beta-Agonists		
Albuterol (spontaneous breathing)	2.5 mg/3 mL saline via nebulizer q 1–4 hours prn	Higher dose (e.g., 5 mg) and continuous nebulizer treatments have not been shown to improve treatment efficacy and should not be routinely used; monitor for tachyarrhythmias and hypokalemia
Albuterol (ventilated patient)	2–4 puffs via ventilator circuit q 1–4 hours prn	
Short-Acting Muscarinic Antagonists		
Ipratropium	500 mcg/5 mL saline via nebulizer q 4 hours prn	The addition of ipratropium to albuterol has not been shown to improve bronchodilation in the setting of AECOPD, but it is safe and often used
Antibiotics (examples)	Dosing variable by antibiotic and adjusted for renal function as necessary Intravenous route preferred if hemodynamic instability or other issues with enteral absorption Duration approximately 5–7 days	Antibiotics most effective if purulent sputum; optimal antibiotic regimen unknown; no antibiotic class has been shown superior in any setting; choice should always cover *H. influenzae, S. pneumoniae,* and *M. catarrhalis* based on local sensitivities; in complicated patients, consider covering pseudomonas and Enterobacteriaceae (e.g., *E. coli,* Klebsiella); narrow coverage based on sputum culture and sensitivities
Uncomplicated* (alphabetical order)		
Amoxicillin/clavulanate		
Azithromycin or clarithromycin		
Doxycycline		
Trimethoprim/sulfamethoxazole		
Complicated* (alphabetical order)		
Cephalosporin, third or fourth generation		
Fluoroquinolones		
Piperacillin/tazobactam		
Glucocorticosteroids		
Methylprednisolone	0.5–1.0 mg/kg IV every 6 hours for 24 hours, then tapering as tolerated to every 12 hours for 24 hours, then once daily	Optimal dosing unknown, but a total duration of less than 2 weeks is recommended; IV and PO steroids are likely equivalent, but IV regimen is generally used in the ICU; initial high doses of steroids should be rapidly tapered as tolerated to reduce the risk of adverse effects
Prednisone	60 mg po daily, then taper	
Oxygen	Titrated to an oxygen saturation of 90%–93%. In hypercapnic patients, check arterial blood gas after 30 minutes	Venturi mask provides more accurate and consistent delivery of oxygen than nasal cannula, but it is more likely to be removed by the distressed patient

*Complicated patients include those with age ≥ 65 years, forced expiratory volume in 1 second (FEV_1) ≤ 50% predicted, ≥ 3 exacerbations in the previous year, concomitant cardiac disease, history of endotracheal intubation, hospital admission or antibiotics in the previous 3 months, or residence in a nursing home or other institutionalized setting.

Side effects of ipratropium include dry mouth, sore throat, nausea, worsening of narrow angle glaucoma, and, rarely, urinary retention.

Methylxanthines (e.g., theophylline, aminophylline) may have a role in management of chronic stable COPD, but they are not recommended in the setting of AECOPD because of mediocre efficacy, an unclear mechanism of action, and a relatively high incidence of adverse

effects, including nausea, vomiting, seizures, tremor, palpitations, and arrhythmias. Further, multiple studies demonstrate no beneficial effect of methylxanthines over standard β_2-agonist and corticosteroid therapy, when used either as a single agent or in combination with β_2-agonists and corticosteroids. Similarly, long-acting beta-agonists (e.g., formoterol, salmeterol) and long-acting muscarinic antagonists (e.g., tiotropium) have a clear role in chronic stable disease but are unproven in acute exacerbation and should not replace their short-acting counterparts.

GLUCOCORTICOSTEROIDS

Steroids (e.g., methylprednisolone, prednisone) decrease the acute inflammation associated with severe AECOPD and thereby improve lung function, decrease treatment failure, and shorten hospital length of stay. The optimal drug, dose, and duration of steroid therapy have not been established. Although a number of studies have shown equivalent efficacy of oral, inhaled, and intravenous steroids in hospitalized patients with AECOPD, these studies generally excluded patients with severe AECOPD admitted to the ICU, and most guidelines recommend the use of intravenous steroids in this setting. Methylprednisolone 0.5 to 1 mg/kg intravenously every 6 hours is a frequently used initial regimen, but tapering to every 12 hours and then every 24 hours over 2 to 3 days as tolerated by the patient is recommended to reduce the risk of acute steroid side effects, such as hyperglycemia, psychosis, insomnia, fluid retention, hypokalemia, and peptic ulceration. Because higher doses of steroids (e.g., methylprednisolone 1.5 to 2 mg/kg every 6 hours) increase the risk of adverse effects and do not improve outcomes, their use is not recommended. After evidencing clinical improvement, the patient may be switched to an oral steroid (e.g., prednisone), to be tapered as tolerated to complete a course of approximately 2 weeks.

ANTIBIOTICS

Given current evidence, antibiotics should be administered to all patients with severe AECOPD, especially in the presence of purulent sputum or need for mechanical ventilation. Antibiotics decrease mortality and treatment failures in severe AECOPD, though their benefit as an addition to steroid therapy has not been proven. As with steroids, the optimal drug, route, and duration of therapy have not been established. The choice of antibiotic should cover the commonly isolated bacterial organisms: *Haemophilus influenzae, Streptococcus pneumoniae,* and *Moraxella catarrhalis,* with consideration given to coverage of *Pseudomonas aeruginosa* and Enterobacteriaceae such as *Escherichia coli* and *Klebsiella pneumoniae* in more complicated cases (see Box 76.1). The antibiotic choice should reflect local resistance patterns whenever possible. Additionally, antibiotic coverage should be narrowed based on the results of sputum culture and antimicrobial sensitivity testing, once those data become available. Although the ideal duration of antibiotic therapy is unknown and likely varies by drug, studies suggest that shorter courses of 5 to 7 days may be as effective as longer courses and less likely to produce side effects.

OXYGEN

Supplemental oxygen should be administered as necessary to maintain an arterial oxygen saturation of approximately 90% to 93%. Higher oxygen saturations should not be targeted, because some patients with COPD will become increasingly hypercapnic when given an excess of supplemental oxygen. This hypercapnic response is partly due to reversal of hypoxic pulmonary vasoconstriction, resulting in greater perfusion of poorly ventilated acinar units with a high carbon dioxide tension. In addition, oxyhemoglobin has a lower affinity for carbon dioxide than deoxyhemoglobin, so that supplemental oxygen dissociates carbon dioxide from hemoglobin with a resultant increase in the carbon dioxide partial pressure in blood (the Haldane effect). Reversal of hypoxic respiratory drive plays only a minor role. Because of the risk of exacerbating hypercapnia, oxygen

should be administered in a controlled fashion in COPD. Venturi mask is generally the preferred delivery system for nonventilated patients, because it delivers a more accurate and constant fraction of inspired oxygen (FIO_2) than nasal cannula, in which the FIO_2 varies depending on the patient's minute ventilation even at constant flow rates. However, severely dyspneic patients may better tolerate nasal cannula rather than a mask over the face. In either case, patients with severe AECOPD should be monitored with continuous pulse oximetry and, at least initially, a repeat arterial blood gas approximately 15 to 30 minutes after any adjustment to the dose of supplemental oxygen. Note that venous blood gases are unreliable for monitoring blood gases in AECOPD. Most importantly, one should never tolerate hypoxemia to prevent hypercapnia; rather, one should always ensure adequate oxygenation and manage consequent acute hypercapnia.

MECHANICAL VENTILATORY SUPPORT

In cases of very severe AECOPD, mechanical ventilatory support may be required to relieve dyspnea, improve gas exchange, and mitigate the morbidity and mortality associated with acute respiratory failure. Mechanical ventilation should be adjusted to gradually correct acute hypercapnia back to the baseline $PaCO_2$ and not to the normal range (see Appendix B). In the short term, overcorrection of $PaCO_2$ in a patient with chronic hypercapnia may result in severe alkalemia and, in the long term, renal excretion of the bicarbonate necessary for buffering chronic respiratory acidosis. This in turn can interfere with liberation from assisted ventilation and weaning of ventilatory support, respectively (see Chapters 4 and 25).

The primary indications for mechanical ventilation are respiratory distress with a nonsustainable pattern of breathing (e.g., rapid shallow breathing, extensive use of accessory muscles, intercostal or supraclavicular retractions with inspiration, or paradoxical motion of the chest and abdomen) or severe or worsening gas exchange with refractory hypoxemia or significant acute respiratory acidosis despite aggressive medical therapy. An arterial pH of < 7.25 with hypercapnia should prompt immediate intervention.

Absent a contraindication, patients requiring ventilatory support for severe AECOPD should first receive a trial of non-invasive ventilation (NIV) via a continuous positive airway pressure mask connected to a pressure-cycled assisted ventilation machine or a standard ventilator (see Chapter 3). Several randomized, controlled trials in patients with acute respiratory failure resulting from AECOPD have shown that NIV is superior to invasive ventilation: NIV relieves symptoms, improves respiratory acidosis, reduces the need for endotracheal intubation, shortens length of hospital stay, and decreases short-term mortality. One significant advantage of NIV is a reduced requirement for sedatives, which may themselves impair ventilation in AECOPD. In addition, NIV is easily stopped and started as necessary for a patient with a waxing and waning course. Patients with lower severity of illness as reflected by lower Acute Physiology and Chronic Health Evaluation (APACHE) II scores, younger age, ability to cooperate, minimal air leak, and evidence of improvement within the first few hours all demonstrate a higher NIV success rate. NIV is *contraindicated* in patients with hemodynamic instability, substantial craniofacial abnormalities, facial burns, impaired consciousness, and high aspiration risk. Additionally, patients with severe respiratory acidosis (pH < 7.10, $PaCO_2$ > 90) are more likely to fail NIV, perhaps because of poor mental status. Carefully monitor all patients started on NIV for cooperation with therapy, and evaluate success by repeat analysis of ABG within 2 hours of initiating therapy to document improvement of respiratory acidosis.

When NIV has failed or is contraindicated, endotracheal intubation with invasive mechanical ventilation is appropriate. Invasive mechanical ventilation is discussed in detail in Chapter 2, but there is one issue specific to obstructive lung disease that deserves comment here. Patients with severe AECOPD are at risk for both dynamic hyperinflation and ventilator-induced lung injury, from the prolonged expiratory time caused by their airflow obstruction. Further, some of their small airways actually collapse during expiration, trapping air in the associated lung regions.

As a result, the lungs do not empty completely before the next ventilator breath arrives, resulting in an incremental rise in lung volume at end-expiration and thus intrinsic positive end-expiratory pressure ($PEEP_i$, or auto-PEEP). When end inspiratory or "plateau" pressure exceeds 30 cm H_2O, patients risk excessive and potentially damaging stretch to the alveoli, causing the release of local and systemic inflammatory mediators. Even with plateau pressures kept below 30 cm H_2O, high tidal volumes can cause stretch injury; hence, tidal volumes of 5 to 7 mL/kg predicted body weight (PBW; see Appendix E for PBW formulas) are recommended to reduce the likelihood of overdistention and ventilator-induced lung injury. ICU patients requiring invasive mechanical ventilation for severe AECOPD should be carefully monitored for $PEEP_i$ with ventilator settings adjusted to minimize its deleterious effects (discussed in detail in Chapters 2 and 75).

Additionally, patients with COPD may have underlying chronic ventilatory failure with a chronic compensated respiratory acidosis at baseline. This manifests as an elevated serum bicarbonate, either at admission or at baseline, which can be used to calculate the patient's baseline $Paco_2$ (see Box 76.1). Overcorrection of Pco_2 in patients with a baseline compensated respiratory acidosis results in acute alkalosis/alkalemia (Appendix B and Chapter 83) and subsequent bicarbonaturia (loss of renal compensation for baseline chronic hypercapnia); consequently, an acidosis occurs when attempting to liberate or wean the patient from mechanical ventilation. To avoid ventilator-induced lung injury and acid-base disturbances, patients should be managed with a goal of maintaining a $Paco_2$ at or above the patient's usual baseline, with a pH target of 7.35 to 7.38.

OTHER INTERVENTIONS

Numerous adjunctive therapies have been tried in severe AECOPD, including chest physical therapy with postural drainage to aid in the mobilization of thick secretions, administration of mucolytic or antioxidative agents such as aerosolized (or direct intra-tracheal injections via endotracheal tube) *N*-acetylcysteine, neuromuscular paralysis to prevent ventilator dyssynchrony, use of a helium-oxygen mixture to decrease airflow resistance, and even heroic measures such as extracorporeal membrane oxygenation (ECMO) and carbon dioxide removal ($ECCO_2R$). However, no controlled studies document the efficacy of any of these treatments for severe AECOPD, and most are associated with potentially deleterious side effects. As a result, none of these interventions is recommended for routine use. As in any ICU patient, however, adjunctive therapies for prophylaxis of common complications such as venous thromboembolism, peptic ulceration, and nosocomial infection are always appropriate (Chapter 12). In addition, for patients who are active smokers, nicotine replacement therapy may help to relieve withdrawal symptoms.

PREVENTION

Although ICU management of acute respiratory failure resulting from severe AECOPD must necessarily prioritize acute, life-threatening issues, it is important to recognize that the admission for critical illness also offers an important opportunity to address preventative measures that may avert subsequent long-term morbidity. During recovery from critical illness, COPD patients who smoke cigarettes may be very receptive to a strong recommendation to quit smoking and to education and guidance regarding both pharmacologic and nonpharmacologic means to aid in successful quitting. In addition, the medical team should ensure that the patient's vaccinations for influenza and pneumococcus are up to date prior to hospital discharge. Given data suggesting that regular outpatient use of long-acting anticholinergics, long-acting beta-agonists, and combination therapies with inhaled corticosteroids and long-acting beta-agonists reduce exacerbation frequency, a careful review of chronic maintenance medications is warranted. In addition, reviewing with patients how they use their outpatient medications and asking them to demonstrate inhaler technique may reveal nonadherence, inappropriate dosing regimens, or suboptimal inhaler technique, all of

which may be corrected with eduction prior to discharge. Recovery from acute respiratory failure also offers a natural opportunity to discuss advanced directives with patients and their families so that they can formally state their preferences for use of life-sustaining therapies if critical illness should recur (Chapters 102 and 104). Lastly, as malnutrition and deconditioning are both highly prevalent among COPD patients recovering from acute respiratory failure, consultation with a clinical nutritionist (Chapter 15) should be requested for COPD patients and their immediate family members and patients should be referred to an outpatient pulmonary rehabilitation program at hospital discharge.

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CHAPTER 77

Deep Venous Thrombosis and Pulmonary Embolism

Nuala J. Meyer ■ Harold I. Palevsky

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are different manifestations of the disease process known collectively as venous thromboembolism (VTE). The presentation of PE in particular can be notoriously variable and nonspecific, especially in critically ill patients in the intensive care unit (ICU) with preexisting reasons for cardiopulmonary compromise. These protean presentations may partly explain why PE remains one of the most frequently unsuspected autopsy findings in deceased ICU patients. This chapter describes the pathophysiology, diagnosis, prognosis, and therapy of VTE in critically ill patients, with extended consideration of the management of massive and submassive PE.

Pathophysiology

Venous thrombosis, whether in the lungs or the deep veins, begins as a microthrombus formation at a site of venous stasis or injury. Clot impedes blood flow, which promotes further vascular injury and extension of the thrombus. Upon propagating to a proximal vein, classically defined as at or above the popliteal vein, the clot may embolize to the pulmonary circulation. The presence of thrombus causes chiefly a mechanical obstruction to circulation, but it also triggers the release of vasoactive and, in the case of PE, bronchoreactive substances like serotonin that can exacerbate ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch. Obstruction in the pulmonary circulation increases right ventricular (RV) afterload, raising RV wall tension and potentially leading to RV dilatation, dysfunction, and ischemia with diminished coronary perfusion. Concomitantly, the PE-induced $\dot{V}/\dot{Q}$ mismatch in the pulmonary circulation contributes to hypoxemia. This combination of increased RV oxygen consumption in the setting of reduced oxygen supply can lead to acute right heart failure, which is the likely cause for sudden death in patients with massive PE.

Acute changes in RV pressure and volume can also compromise the left heart. As the RV distends and stiffens, the interventricular septum can flatten or even bow into the chamber of the left ventricle (LV), altering the LV diastolic pressure–volume characteristics. This phenomenon can be detected echocardiographically, and it is often referred to as the "D sign" because the normally round parasternal short axis view of the LV takes on a "D" shape that results from the flattened interventricular septum. In patients with a patent foramen ovale (PFO), the acute rise in right atrial and ventricular pressures can result in shunting of blood across the atria from right to left. This situation may manifest as profound oxygen-refractory hypoxemia or as a paradoxical embolus from clot originating in the venous circulation traveling across the PFO to cause an arterial occlusion (such as an embolic stroke).

Although the most life-threatening complications of PE typically stem from cardiovascular compromise, PE also impairs gas exchange. This occurs chiefly through the creation of increased

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physiologic dead space in the unperfused or underperfused segments of the pulmonary circulation. Rising dead space typically manifests as an increase in minute ventilation and tachypnea, but it may also be recognized by a rise in the arterial partial pressure of carbon dioxide ($Paco_2$) or a $Paco_2$ that is abnormally "normal" despite increased minute ventilation. For example, an arterial blood gas (ABG) with a "normal" $Paco_2$ = 38–40 mm Hg when a patient is breathing more than 30 times per minute should be recognized as abnormal and highly consistent with PE or another process increasing dead space. $\dot{V}/\dot{Q}$ mismatch results in hypoxemia that tends to respond well to modest supplemental oxygen. Severe, oxygen-refractory hypoxemia is rare and suggests either significant circulatory compromise (shock) causing a low mixed venous oxygen saturation, right-to-left shunting across a PFO, or a superimposed pulmonary process such as chronic obstructive pulmonary disease (COPD) or pneumonia.

Risk Factors

Critical illness, with its resultant immobility and frequent vascular injury, is a significant risk factor for VTE and a recognized indication for prophylaxis, discussed at length in Chapter 12. In addition, well-defined acquired risk factors (Table 77.E1) include advanced age, malignancy, vascular injury resulting from surgery or trauma, spinal cord injury, pregnancy and the postpartum period, obesity, COPD, immobility, certain medications, indwelling vascular catheters, and prior VTE. Risk factors may also be heritable thrombophilias, such as genetic deficiencies in protein C or S, any of the antiphospholipid antibody syndromes, or the factor V Leiden mutation, which is the most common genetic risk factor. The presence of one or more risk factors is highly relevant in assessing patients with possible VTE and is included in diagnostic scoring systems.

Clinical Presentation

DVT symptoms are relatively straightforward. Pain or swelling in the calf or thigh are the hallmarks of lower extremity DVT. For DVT of the upper extremity, which is far less common in the overall population with VTE but constitutes a noteworthy proportion of DVT in critically ill patients, most cases (> 75%) are associated with indwelling catheters, cardiac devices (pacemakers/defibrillators), or cancer. Upper extremity swelling or erythema may be present, but occasionally upper extremity clots only come to attention by an inability to catheterize a central vein or by the failure of a central line to infuse or draw back. Although a smaller proportion of patients with acute upper extremity DVT, as compared to lower extremity DVT, present with symptomatic PE, the incidence of PE during the subsequent 3 months is similar regardless of DVT location, and thus the duration of anticoagulation treatment should be the same regardless of location.

The clinical presentation of PE is notoriously variable and nonspecific. Nonetheless, results from the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) trial, involving more than 800 subjects with suspected PE, point to dyspnea, pleurisy, and leg pain as the most common presenting symptoms. Most patients with PE present with dyspnea, frequently rapid in onset, while for almost 20% of patients, dyspnea is only present on exertion and for others it is most pronounced while lying supine (orthopnea). Pleuritic pain is frequent (40% of patients), but nonpleuritic chest pain may also occur. Wheezing or cough is present in almost a third of patients and is more common in patients with preexisting cardiopulmonary disease. Hemoptysis is uncommon, and when it occurs it tends to be scant; none of the almost 200 subjects with PE in the above-mentioned study had more than one teaspoon of blood. Calf or leg symptoms were present in ~40% of subjects, similar to the first PIOPED study. Compared to those under 70 years of age, patients 70 years or older with PE are more likely to report pleuritic chest pain and leg symptoms. Notably, critically ill patients were excluded from the PIOPED II trial, and are more problematic to characterize with PE as they tend to have competing explanations for dyspnea, chest pain, or cardiopulmonary embarrassment.

TABLE 77.E1 ■ **Risk Factors for Venous Thromboembolism (VTE)**

Epidemiologic	Stasis	Vascular Injury	Hypercoagulability
Critical illness	Immobility	Trauma	Factor V Leiden mutation
Prior VTE	Paralysis	Surgery	Antiphospholipid antibody syndrome
Advanced age	Prolonged travel	Indwelling central venous/pulmonary artery catheters	Protein C, S, or antithrombin III deficiency
Malignancy (adenocarcinoma)	Leg casts	Postpartum	Polycythemia
Congestive heart failure (CHF)	Pregnancy		Heparin-induced thrombosis
Obesity			Pregnancy/postpartum
Chronic obstructive pulmonary disease (COPD)			Hormonal (estrogen-progestin) therapy
Nephrotic syndrome			Oral contraceptives
Cigarette smoking			Macroglobulinemia

The most common signs of PE include tachypnea ≥ 20 breaths per minute (~half of patients), tachycardia ≥ 100 beats/minute (25%), and calf or leg findings (swelling, erythema, tenderness, or a palpable cord; 45%). More than one third of PE patients in the emergency room will have a normal Pao_2 (≥ 80 mm Hg). Most patients demonstrate an increased alveolar-to-arterial (A-a) gradient when measured, but severely widened A-a gradient is rare. Respiratory alkalosis caused by hyperventilation is typical, although this finding is difficult to adapt to the critically ill population presenting with respiratory failure. Presentation with shock or circulatory collapse is infrequent, occurring in fewer than 10% of all PIOPED II subjects. Interestingly, presentation with shock was no less frequent in subjects without preexisting cardiopulmonary disease compared to those with such comorbidities. Diaphoresis, cyanosis, or fever ≥ 38.5° F are uncommon presentations for PE. In contrast, an abnormal cardiac examination (elevated jugular venous pulsation, increased pulmonic component to the second heart sound [P_2], or an RV lift), though present in only one fifth of patients, helped to discriminate patients with PE from those without. Lung examination is abnormal in approximately a third of patients with PE, with crackles or decreased breath sounds being the most common findings and pleural rubs being distinctly uncommon. Lung exam did not help to distinguish those with PE from those without, unlike abnormal cardiac examination findings.

Because the symptoms and signs of PE remain nonspecific, the history and exam alone are rarely sufficient to adequately make or exclude the diagnosis, even when the patient is an excellent historian. By virtue of their critical illness, ICU patients are frequently unable to communicate their symptoms and have numerous potential explanations for observed tachypnea or tachycardia, making the diagnosis even more challenging. In addition, unstable patients are often poor candidates for immediate transport to a more definitive diagnostic procedure, and they may have organ dysfunction such as renal insufficiency that make such procedures problematic. The contributions of various tests in evaluating suspected PE are described in this chapter. Figure 77.1 presents an algorithm for approaching the diagnosis of VTE in critically ill patients.

Diagnosis

CLINICAL PREDICTION RULE: WELLS CRITERIA

Failure to diagnose PE is a serious management error, as a portion of untreated patients may die. A clinical decision rule (Table 77.1) known as the Wells criteria helps to risk stratify patients

TABLE 77.1 ■ **Wells Clinical Decision Rule for Pulmonary Embolus***

Variable	Points Assigned
Clinical signs/symptoms of DVT	3.0
Alternative diagnosis *less* likely than PE	3.0
Heart rate > 100/minute	1.5
Immobilization > 3 days *or*	1.5
Surgery in previous 4 weeks	
Previous VTE	1.5
Hemoptysis	1.0
Malignancy	1.0
Risk Estimates*: Low Risk = < 2; Moderate Risk = 2-6; High Risk = > 6.	

*Data from Wells PS, Anderson DR, Stiell RM, et al: Ann Intern Med 135:98-107, 2001.
DVT, deep venous thrombosis; VTE, venous thromboembolism; PE, pulmonary embolism.

with suspected PE to avoid unnecessary testing in low-risk patients. This rule has been extensively tested and validated in stable patients, both hospitalized and ambulatory. The Wells criteria assign points based on clinical signs and symptoms of DVT or PE, risk factors of the patient (prior VTE, malignancy, immobility), and the presence or absence of an alternative explanation for the patient's clinical deterioration. When anticoagulation was withheld based on a low (< 2) Wells score and a negative D-dimer level, the incidence of VTE in the subsequent 3 to 6 months was < 1%. Although the Wells criteria have not been tested in critically ill populations, its central tenets—assessing the patient's global risk for PE based on patient historical factors, clinical presentation, and differential diagnosis—remain a rational approach to initial risk stratification.

PLASMA BIOMARKERS: D-DIMER, TROPONIN, AND BRAIN NATRIURETIC PEPTIDE (BNP)

In low-risk patients with suspected PE, a normal D-dimer level identifies a subgroup in whom it appears safe to withhold anticoagulation. In 3000 noncritically ill subjects with suspected PE, withholding further testing for PE and anticoagulation for a Wells score < 2 and a normal D-dimer level led to a rate of VTE occurrence in the subsequent 3 months of only 0.5%. In subjects considered to be at moderate or high risk for PE, D-dimer testing has not proven helpful and thus is not recommended. In addition, just as D-dimer is frequently elevated by surgery, pregnancy, or a comorbid illness such as cancer, critical illness and activation of the coagulation system may elevate D-dimer in the absence of thromboembolic phenomena. Use of a D-dimer in evaluating an ICU patient's risk for PE should thus be restricted to low-risk patients. Cardiac-specific biomarkers such as troponin or brain natriuretic peptide (BNP) are neither sensitive nor specific enough to be used to diagnose PE, but troponin in particular may be useful in risk stratifying a patient and deciding on the level of therapy, as discussed later.

Other Non-invasive Studies

In critically ill trauma patients, the combination of a 10% fall in pulse oximetry saturation and preserved static lung compliance proved to be both sensitive and specific in evaluating patients for PE. Electrocardiogram (ECG) is helpful in suggesting other potential etiologies for chest pain or dyspnea and may demonstrate signs of acute RV strain (incomplete or complete right bundle-branch block, T-wave inversions in the anterior precordium, or an S wave in lead I with a Q-wave and T-wave inversion in lead III [$S_1Q_3T_3$ sign]), though these findings are not specific for PE. (For more information, go to www.expertconsult.com.)

Ultrasonography

Both ultrasonography and impedence plethysmography (IP) are highly sensitive and specific tests for symptomatic DVT. Ultrasonography has essentially supplanted IP, with widespread use and reported positive and negative predictive values approaching 100% in patients with symptomatic lower extremity DVT. In asymptomatic patients, including those with no leg complaints but presenting with PE, clots are more likely to be distal; serial ultrasound examinations (separated by ~1 week) may document clot extension. The utility of ultrasound for upper extremity DVT seems to be equally good when clots are symptomatic; contrast venography is the diagnostic standard if ultrasound is inconclusive.

Echocardiography

Echocardiography is an attractive tool for the critically ill patient with suspected PE given its portability and non-invasiveness. Unfortunately, echocardiography is insensitive in the detection of PE

and cannot be used as an individual diagnostic study. In prospective trials of unselected patients with suspected PE, the sensitivity of transthoracic echocardiogram (TTE) ranged from 29% to 52%. However, certain echocardiographic findings are specific for PE, the best of which is the McConnell sign, described as RV-free wall hypokinesis or akinesis coupled with normal or hyperkinetic RV apex performance. At least two studies have reported specificities ≥ 96% for this finding. However, this sign is uncommon and carries only 16% sensitivity, so failure to detect this finding does not exclude PE. Likewise, echocardiographic visualization of clot in the right atrium, RV, or pulmonary artery (via the transesophageal probe) clinches the diagnosis of PE, though this occurs infrequently. Other helpful criteria include elevations in the ratio of RV to LV end diastolic dimensions (≥ 0.7), the ratio of RV area: LV area ≥ 0.66, or the "D sign" or interventricular septal shift, with specificities in the 75% to 85% range. It is worth emphasizing that ventilated patients with severe hypoxemia and widespread hypoxic pulmonary vasoconstriction (e.g., those with the acute respiratory distress syndrome [ARDS]) also can demonstrate echocardiographic criteria of acute RV strain or failure, so that this finding is not specific. Because the chest radiograph for patients with PE is rarely associated with the dense airspace consolidation characteristic of hypoxemic respiratory failure, a good practice is to interpret right ventricular echocardiogram findings in the context of the chest radiograph. If the right heart strain is marked and the chest radiograph reveals dense consolidation and the patient is hypoxic, hypoxemic respiratory failure is the likely cause of the echocardiographic findings. In contrast, severe right heart strain in the absence of airspace filling on chest radiograph is highly suspicious for a PE.

As discussed in further detail later, the echocardiographic demonstration of RV dysfunction reliably predicts an increased risk of fatal PE and thus plays a role in risk stratification for the management of critically ill patients with PE. However, controversy remains as to whether the detection of RV dysfunction should change or escalate the management of PE. There is near consensus that the documentation of RV strain in the setting of PE should at a minimum prompt ICU management of the patient with close observation for possible deterioration.

Chest Radiographic Studies

CHEST RADIOGRAPH AND CHEST COMPUTED TOMOGRAPHY

While the chest radiograph is often abnormal in the presence of PE, there is no sensitive or specific finding that confirms or rules out PE. The three "classic" findings of Hampton's hump (a peripheral wedge-shaped opacity resulting from infarction), Westermark's sign of focal oligemia, or Palla's sign of an enlarged right descending pulmonary artery are all notably uncommon. Platelike atelectasis, subtle areas of volume loss, or indistinct opacities are common, but the chest radiograph may also be completely normal.

Computed tomographic angiography (CTA) (i.e., CT angiography) has largely become the diagnostic standard for PE. Although not perfect, a CTA can be very helpful when used in the context of a patient's pretest clinical probability for PE. As demonstrated by the PIOPED II study, when the clinical probability for PE is intermediate or high, a positive CTA has a very high positive predictive value of 92% to 96%. Similarly, a negative CTA has an excellent negative predictive value of 89% to 96% when the clinical probability is either low or intermediate.

However, the diagnostic accuracy falls when the finding of a CTA is *discordant* with the clinical probability. Among low probability patients, 42% of positive CTAs are actually "false positive" with respect to the reference standard. Consensus opinion is to treat such patients only if they have main or lobar pulmonary arterial involvement and to consider additional testing (repeat ultrasonography, ventilation-perfusion scan, or CT venography) for segmental or subsegmental defects. Among high-probability patients, 40% of negative CTA scans were "false negative" (i.e., positive by the reference standard). Thus, when clinical probability is high (Wells score > 6), a negative CTA essentially mandates further testing to exclude PE. In this instance, PIOPED II investigators

Another potentially useful parameter is the alveolar dead space fraction (AVDSf), calculated by measuring the difference between arterial and end-tidal CO_2: [AVDSf = ($Paco_2$ – $ETCO_2$)/$Paco_2$]. As dead space rises, $ETCO_2$ no longer approximates $Paco_2$ because no gas exchange is occurring across the vascular beds distal to the embolus, and thus $ETCO_2$ falls. Unless minute ventilation increases, $Paco_2$ will rise progressively until a new steady state is reached (see Chapter 1). One study of hospitalized but noncritically ill patients reported that an AVDSf < 0.15 excluded PE with a sensitivity of > 97% and a negative predictive value of 98%. However, using AVDSf as a diagnostic test for PE is not recommended for ICU patients because they often have other reasons for increased alveolar dead space (see Appendix B for examples) and questions arise related to the accuracy and precision of measurements of $ETCO_2$ as there often is no alveolar plateau in the expiratory capnographs. Nevertheless, an increased AVDSf lends support to a potential PE diagnosis, whereas a very low AVDSf argues against a large perfusion defect.

recommend anticoagulation based on the high clinical probability while obtaining additional testing (extremity ultrasonography, magnetic resonance venography, potentially ventilation-perfusion scanning, or digital subtraction angiography).

VENTILATION: PERFUSION SCANS

The ventilation-perfusion ($\dot{V}/\dot{Q}$) scan, traditionally the diagnostic test of choice in PE, has almost entirely been supplanted by CTA in the modern era. The major difficulty with $\dot{V}/\dot{Q}$ scanning is the large proportion of scans interpreted as either intermediate probability (i.e., with a 40% likelihood of PE) or indeterminate (unknown risk of subsequent PE). In addition, performing the ventilation component of a $\dot{V}/\dot{Q}$ scan is technically challenging for mechanically ventilated patients. Therefore, in practice $\dot{V}/\dot{Q}$ scans are reserved for patients with a normal or near-normal chest radiograph *and* a contraindication to CTA (such as renal insufficiency, sensitivity to intravenous [IV] contrast), or a relative contraindication to chest radiation (such as pregnancy). For both of these patient groups, a wise choice is to perform a perfusion lung scan alone (without ventilation images), which cuts the radiation exposure in half, does not require contrast, and can effectively exclude PE if normal.

PULMONARY ANGIOGRAPHY

Digital subtraction angiography (DSA) remains the "gold standard" by which most clinical trials judge PE diagnosis, although even DSA is subject to variable operator performance when evaluating segmental and subsegmental clots. Other disadvantages to DSA include its invasive nature with 0.2% mortality, and the potential for a large radiation exposure. Mortality from DSA may be most relevant in patients with elevated pulmonary systolic presume (> 70 mm Hg) or right ventricular end diastolic pressure (> 20 mm Hg). Invasive angiography remains an option for the patient with a high clinical probability of PE in whom other diagnostic modalities fail to yield a diagnosis or empiric treatment carries great risk.

Risk Assessment

The clinician remains faced with many decisions after diagnosing VTE. Although anticoagulation is the mainstay of therapy, decisions persist regarding anticoagulant selection, consideration of thrombolytic therapy or invasive procedures, and therapy duration. Thus, a risk assessment at the time of treatment initiation is prudent.

Patients with PE who present in shock are at high risk for death. Often termed "massive PE," the acute mortality may be as high as 65%. Such patients obviously require immediate stabilization in the ICU and rapid anticoagulation. Unless a strong contraindication exists (Box 77.1), thrombolytic therapy should be promptly administered to such patients (Figure 77.1).

A subset of patients with PE present without clinically overt signs of systemic hypoperfusion or hypotension, but testing reveals a high risk for progressing to shock or death (Figure 77.1). The term *submassive PE* has been applied in this situation. The best evidence for risk stratifying these patients comes from echocardiographic studies documenting acute right ventricular strain in the setting of a confirmed PE. Moderate RV dysfunction on echocardiography confers a two- to sixfold increased risk of in-hospital death compared to normal RV function. Approximately 10% of patients with normal blood pressure but RV dysfunction progress to overt shock, and RV wall motion abnormalities predict recurrent pulmonary embolism. Two clinical trials to test the efficacy and safety of thrombolytic therapy in patients with submassive PE had conflicting results, and no trial showed a mortality benefit from thrombolytics. Thus, it remains premature to recommend a change in therapy based on echocardiographic findings alone. At a minimum, the detection of RV dysfunction in the setting of PE is a good indication for ICU admission.

BOX 77.1 ■ Absolute and Relative Contraindications for Thrombolytic Therapy

Absolute

Active intracranial or internal hemorrhage
Known intracranial neoplasm, aneurysm, or arteriovenous malformation
Significant head trauma
Known bleeding diathesis
Intracranial, spinal, or ophthalmologic surgery within 3 months
Cerebrovascular accident within 2 months
Known hypersensitivity (if streptokinase to be used, prior streptokinase use < 6 months)

Relative

Uncontrolled hypertension
Pregnancy
Recent (7 to 10 days) trauma or major surgery (includes cardiopulmonary resuscitation [CPR])
Advanced age
Liver disease
Diabetic retinopathy
Venipuncture or arterial puncture at noncompressible site

Cardiac biomarkers, in particular troponin, may also aid in risk stratification of patients with PE. Cardiac troponins correlate with the extent of RV dysfunction, and several studies reported that normal levels of troponin have a high negative predictive value for in-hospital mortality from PE. For a hemodynamically stable patient with RV dysfunction and a negative troponin level, some authors advocate against using thrombolytic therapy. However, the rise in circulating troponin may not occur for 6 to 12 hours after RV ischemia, tempering the utility of troponin. While BNP also correlates with the degree of RV dysfunction and rises with RV injury, validated cutoffs for "positive" and "negative" BNP levels are lacking in the setting of PE.

Clinical deterioration of a patient with PE receiving therapeutic anticoagulation is an ominous sign. When a previously stable patient with PE progresses to shock, right ventricular ischemia and failure is the most likely diagnosis. In addition to supportive measures, a re-evaluation of the anticoagulant strategy is warranted (Figure 77.1). Most clinicians would escalate to thrombolysis, either medically, surgically, or via invasive catheters. If deterioration takes the form of acute hypoxemia with apparently preserved perfusion, attention should focus on a possible right-to-left shunt (via a PFO), a very low mixed venous oxygen saturation due to interventricular dependence (resulting in low cardiac index), or infarction-related atelectasis of a lobe or lung.

Treatment

SUPPORTIVE CARE: OXYGEN, FLUID, AND VASOACTIVE THERAPY

Mechanical ventilation—via either a non-invasive mask or an endotracheal tube—may be necessary to support a patient's increased minute ventilation, especially for those patients presenting with shock. However, the fluid management of a patient with respiratory failure or impending shock from PE can be complex. Close attention to adequate preload prior to intubation is paramount, as the failing right ventricle may not tolerate a dramatic decline in preload during intubation and the institution of positive pressure ventilation. A trial of non-invasive ventilation (see Chapter 3) to unload some of the work of breathing may be worthwhile to assess the RV response to positive pressure. Prior to standard intubation, one should ensure adequate right-sided filling pressures. This can be done empirically by echocardiography or by monitoring central venous pressure (CVP)

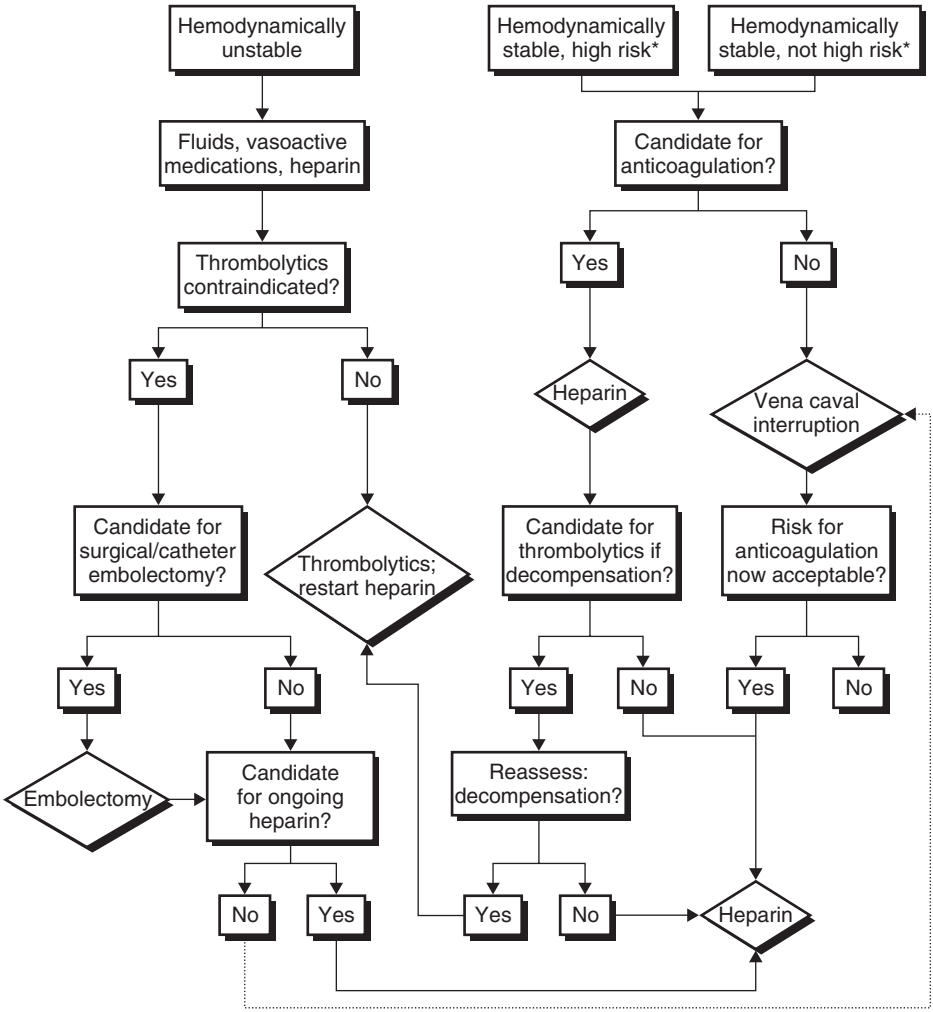


Figure 77.1 Treatment algorithm for confirmed pulmonary embolism according to risk stratification. *High risk refers to being at high risk of decompensating clinically leading to shock or death. (See "Risk Assessment" section in text for details).

waveform, though no absolute consensus exists for what constitutes an adequate CVP. There is also risk from overdistention of a failing right ventricle, whereby increased volume administration decreases RV contractility and increases RV oxygen consumption. In addition, RV overdistention may worsen interventricular bowing toward the left ventricular cavity, compromising LV filling and thus potentially causing diastolic dysfunction and lowering cardiac output. The complex physiology of a decompensating patient with massive PE mandates strong communication between the individuals coordinating the airway and circulation.

No randomized clinical trials of vasoactive support for a patient with massive PE are available to guide therapy. The most promising human data have been reported with dobutamine, a positive inotrope that typically raises cardiac output, decreases pulmonary vascular resistance, and increases oxygen delivery. In some cases, dobutamine decreases arterial PO_2, presumably from

TABLE 77.2 ■ **Dosing of Common Standard Anticoagulants**

Heparin	Bolus: 80 units/kg IV
	Maintenance: 18 units/kg/h IV, adjust to aPTT ≥ 1.5 times baseline
Enoxaparin	1 mg/kg SC 12h (adjust for renal function)
	Monitor anti-Xa levels in obese, very thin, and renal insufficiency
Fondaparinux	7.5 mg SC 24h (5 mg SC if < 50 kg; 10 mg if > 100 kg)
	Do not use if creatinine clearance < 30 mL/min
Argatroban	0.5–1.0 mcg/kg/min IV (adjust for hepatic function)
	Goal: aPTT 1.5–3 times baseline; keep aPTT < 100 s
Lepirudin	0.05–0.10 mg/kg/h IV (adjust for renal function)
	Goal: aPTT 1.5–2.5 times baseline
Rivaroxaban	15 mg oral twice daily x 3 weeks, then 20 mg/day. Take with food
	Do not use if creatinine clearance < 15 mL/min

aPTT, activated partial thromboplastin time.

worsened $\dot{V}/\dot{Q}$ mismatch, but the oxygen delivery benefit derived from augmented cardiac output usually offsets any decrease in saturation. Norepinephrine, a predominant vasoconstrictor with some β_1-agonist inotrope activity, would be the next choice for vasoactive medication based on animal studies, in which norepinephrine was superior to volume therapy, isoproterenol, or placebo. Norepinephrine increases aortic pressure and thus augments coronary blood flow, although at the expense of increasing pulmonary vascular resistance and hence right ventricular afterload.

STANDARD ANTICOAGULATION

Unfractionated heparin is the mainstay of therapy for critically ill patients with PE. For most patients, this remains true even in the era of low-molecular-weight fractionated heparins, fondaparinux, and rivaroxaban, which have advantages over unfractionated heparin including greater bioavailability, more predictable and convenient dosing often without the need for monitoring, and a lower incidence of heparin-induced thrombocytopenia with thrombosis. However, critically ill patients may need further invasive procedures or may be at high risk for bleeding complications, and thus the ability to rapidly reverse anticoagulation is important. Reversibility is most easily achieved with unfractionated heparin. Dosing for heparin and heparin alternatives is presented in Table 77.2. The goal is to achieve therapeutic anticoagulation as quickly as possible, as the failure to achieve aPTT ≥ 1.5 times baseline within 24 hours results in a 15-fold increased risk of recurrent VTE. Although the consensus statement of the American College of Chest Physicians (ACCP) recommends initiating oral vitamin K antagonists (typically warfarin) on the first day of treatment, ICU clinicians generally delay the institution of oral anticoagulation for patients in the ICU until the patient's trajectory is more clearly established in the recovery direction.

HEPARIN ALTERNATIVES

When considering all patients with PE, fondaparinux (a factor Xa inhibitor) and low-molecular-weight heparins (LMWHs: enoxaparin, dalteparin, tinzaparin) have excellent data to support their use as first-line agents for the treatment of PE (see Table 77.2). As mentioned, these medications have less stringent monitoring requirements than heparin, although monitoring of antifactor Xa

activity is recommended for patients who are obese (> 150 kg), very thin (< 40 kg), pregnant, or who have renal insufficiency. Fondaparinux should not be used in cases of severe renal insufficiency. Neither LMWHs nor fondaparinux has specific antidotes to reverse their anticoagulation, although some LMWHs will respond at least partially to protamine sulfate. This, combined with the relatively longer half-life for these agents, make unfractionated heparin the practical first-line agent for most ICU patients. However, in patients without increased risk for bleeding, either LMWHs or fondaparinux may be a good alternative. Rivaroxaban, an oral factor Xa inhibitor, was also recently approved for both acute and maintenance therapy of PE, and may be reversible with either prothrombin complex concentrate or dialysis. It should not be used for patients with renal insufficiency.

For patients with heparin-induced thrombocytopenia (HIT) with thrombosis, several options for anticoagulation exist. Fondaparinux or rivaroxaban are options for patients who have preserved renal function. Two direct thrombin inhibitors, argatroban or lepirudin, are also available. Lepirudin, excreted by the kidney, must be dose-adjusted for renal function. In addition, because of a very high risk for bleeding with lepirudin (up to 18%) in the treatment of HIT, many decrease the approved dose to 0.05 to 0.10 mg/kg per hour. Argatroban, which undergoes hepatic metabolism, should be avoided for patients with hepatic insufficiency. However, data from acute coronary syndrome trials support a bleeding risk with argatroban equivalent to historical controls (i.e., heparin). LMWHs cannot be safely used if a patient has documented HIT, as the antibodies can cross-react with every commercially available LMWH. The newer, oral direct thrombin inhibitors are not approved for use in patients with PE.

RISK OF BLEEDING AND TREATMENT

Whether used for prophylaxis or treatment, unfractionated heparin is associated with an increased risk of bleeding. Most clinical trials using therapeutic IV unfractionated heparin for the treatment of VTE cite a 2% to 3% rate of "major hemorrhage," variably defined as the need for blood transfusion, intracranial bleeding, or estimated bleeding > 1 liter. In less selected settings, where the risk of bleeding may be greater, bleeding rates can approach 12%, with the majority occurring from the gastrointestinal or urinary tract. Intracranial hemorrhage is rare but well recognized. Most clinical trials cite bleeding rates of 1% to 2% for both LMWHs and fondaparinux, lower than that for IV unfractionated heparin. There is a high rate of bleeding, 18%, with the approved dose of lepirudin (continuous infusion of 0.15 mg/kg/h); newer recommendations decrease the dose to 0.05 to 0.10 mg/kg/h. The rate of bleeding with argatroban (3% to 6%) is comparable to that of unfractionated heparin.

In the event of major or life-threatening hemorrhage, heparin (and to a lesser extent, LMWHs) can be neutralized with protamine sulfate. With any anticoagulant, cessation of the administration (at least temporarily) is critical in the treatment of the bleeding patient. Fondaparinux and danaparoid are not reversed by protamine. Because circulating heparin, LMWH, and fondaparinux act as antithrombin III inhibitors, transfusion of fresh frozen plasma is usually relatively ineffective in the face of major hemorrhage. Protamine sulfate only partially neutralizes LMWHs because of the reduced sulfate charges on LMWHs relative to heparin. Enoxaparin is the most resistant to protamine, whereas tinzaparin is the most sensitive. The dose of protamine depends on the level of circulating heparin and the time since the dose was given; if severe hemorrhage immediately follows a heparin bolus, the dose would be 1 mg protamine per 100 units of heparin for complete neutralization. For the more common situation, in which heparin infusion has been ongoing, the dose of protamine is calculated to half-correct the estimated circulating heparin, estimating a half-life of heparin of ~90 minutes. The rationale to half-correct stems from the fact that protamine itself has anticoagulant properties. In addition, protamine can cause an anaphylactoid reaction, with hypotension, bradycardia, shock, dyspnea, and pulmonary hypertension. Administering protamine very slowly, at least 1 minute per 5 mg, reduced the risk of this anaphylactoid reaction. As mentioned,

fresh frozen plasma may not be efficacious in the setting of heparin, LMWHs, or fondaparinux; some case reports cite good outcomes using recombinant factor VIIa. Direct thrombin inhibitors such as argatroban or lepirudin lack specific antidotes, but again case reports cite successful treatment of hemorrhage and in some case, normalization of bleeding parameters, with exogenous factor repletion, recombinant factor VIIa, or both.

THROMBOLYTIC THERAPY

Thrombolytic agents activate plasminogen and thus the fibrinolytic system, rapidly lysing clot. Thrombolytic therapy more rapidly degrades clot than the endogenous fibrinolytic system, and improves hemodynamics from PE. However, seven days after a PE, survivors treated with heparin versus thrombolytic therapy exhibit no difference clinically or when evaluated by perfusion imaging. Because thrombolytic agents clearly increase the risk for life-threatening hemorrhage relative to heparin, clinicians are often uncertain whether rapid clot lysis is warranted. If there is hemodynamic instability or shock, thrombolytics have a clear evidence base to support their use. In a very small clinical trial, eight patients with PE and hypotension were randomized to treatment with heparin alone or streptokinase followed by heparin. All four patients receiving heparin alone died, whereas there were no deaths in the streptokinase group. Uncontrolled studies report successful resolution of shock for over 70% of patients treated with thrombolytics, and thrombolytics appear to improve right ventricular performance and to decrease short-term recurrence of VTE when compared to heparin alone. Thus, for patients with shock and confirmed PE, thrombolytic therapy (see Table 77.3) is warranted (Figure 77.1) unless a strong contraindication exists (see Box 77.1).

In patients with submassive PE (normal hemodynamics but right ventricular dysfunction or "radiographically massive" clots [saddle emboli]), the benefit of thrombolytic therapy is far less certain. A retrospective cohort of patients with submassive PE found thrombolysis significantly improved lung perfusion scans, but deaths (four patients) and intracranial hemorrhage (3%) only occurred in patients treated with thrombolytic agents. A randomized clinical trial comparing heparin alone versus heparin plus alteplase for submassive PE revealed no difference in mortality or recurrent PE. Thus, no definitive trial proves the efficacy of thrombolytic therapy in patients with PE and preserved hemodynamic function. The decision to use thrombolytics necessitates an individualized risk-benefit assessment for each patient, and it is recommended that all patients with PE undergo a risk stratification and assessment for thrombolytic therapy (see Figure 77.1) early in their presentation, to aid later decision-making should the patient deteriorate.

The main risk of thrombolytic therapy is bleeding. As potent activators of the fibrinolytic system, thrombolytics lyse clot anywhere in the vasculature so major bleeding tends to be more common than with anticoagulants. Although individual clinical trials report major bleeding rates as low as 1%, pooled data of randomized trials for PE report a trend toward increased major bleeding (9% versus 6% in heparin) and significantly increased minor bleeding (> 20%) after thrombolytics. In addition, because the strict exclusion criteria in clinical trials limit the risk

TABLE 77.3 ■ **Thrombolytic Dosing for Life-Threatening Pulmonary Embolism (via Peripheral IV)**

Alteplase (rtPA)	10 mg bolus, followed by 90 mg over 2 hours Resume heparin drip
Urokinase	4400 units/kg over 10 minutes, then 4400 units/kg/h over 12 hours Resume heparin drip
Streptokinase	25,000 units over 30 minutes, then 100,000 units/h over 24 hours Resume heparin drip

of hemorrhage, the "real-world" experience with thrombolytics suggests an even greater risk of bleeding. A registry of more than 2000 patients with acute PE reported a major bleeding rate of almost 22% in the 300 patients treated with thrombolytics, with 3% demonstrating intracranial hemorrhage. Box 77.1 lists generally accepted absolute and relative contraindications to thrombolysis. In situations involving a relative contraindication, an individualized risk-benefit analysis should be performed, preferably including the patient (or surrogate decision maker).

Local administration of thrombolytic therapy—for example, via a pulmonary artery catheter—confers no additional clinical benefit or any reduction in complications, relative to standard IV administration. Similar rates of bleeding are observed, and the pulmonary arterial approach produces a major venous puncture for access, which is then at increased risk for hemorrhage. Therefore, standard IV dosage should be used.

MECHANICAL THROMBOLYSIS (SURGICAL OR CATHETER EMBOLECTOMY)

In patients warranting thrombolysis but are felt to be too high risk for bleeding complications, or in patients following unsuccessful thrombolysis, one should consider mechanical solutions to PE. Both surgical embolectomy—typically performed via cardiopulmonary bypass—or percutaneous catheter–based fragmentation or extraction may be beneficial in selected patients when local expertise is present. Although case reports describe dramatic clinical improvements for individual patients, no firm evidence base supports either the surgical or interventional approach over standard anticoagulation, and usually these procedures are reserved for patients with massive PE.

MECHANICAL THROMBOLYSIS (SURGICAL OR CATHETER EMBOLECTOMY)

Surgical embolectomy is considered appropriate for patients with a large clot burden visualized in the right atrium or ventricle, across a patent foramen ovale, or in the proximal pulmonary arterial trunk (saddle embolus). Operative success is highly dependent on operator and site experience, with some suggestion of better outcomes if performed prior to developing overt cardiogenic shock. Also, outcomes appear better if the procedure can be accomplished without bypass or cold cardioplegia.

Interventional catheterization techniques have been developed that allow mechanical fragmentation of thrombus via a standard pulmonary arterial catheter, clot pulverization with a rotating basket catheter, percutaneous rheolytic thrombectomy, or pigtail rotational catheter embolectomy. These techniques aim to rapidly decrease pulmonary vascular resistance and thus alleviate right ventricular dysfunction. In practice, catheter embolectomy rarely results in a massive clot extraction but more commonly allows modest clot fragmentation and either suction removal of fragments or distal displacement of clot.

Both catheter techniques and surgical embolectomy appear more successful when combined with anticoagulation. The ACCP recommendation for either surgical or catheter embolectomy is graded 2C (weak recommendation, low-quality evidence) when patients are deemed unsafe for thrombolytic therapy.

VENA CAVAL INTERRUPTION

Inferior vena caval (IVC) interruption (VCI) devices have a limited role for the treatment of VTE in the patient who cannot safely undergo anticoagulation or has suffered recurrent PE despite adequate anticoagulation. Because the majority of thromboemboli originate in the pelvic or leg veins, VCI has the potential to limit subsequent embolization. In a randomized trial in which all patients received 3 months of anticoagulation for DVT and half were randomized to receive VCI,

the rate of PE was significantly reduced in the short term (< 1 month), but the rates of PE, death, or major bleeding were unchanged in the long term (2 years). In addition, VCI likely increases the risk for recurrent lower-extremity DVT by contributing to IVC stasis. Retrievable or temporary IVC filters are attractive for patients with a short-term contraindication to anticoagulation, such as those who require surgery, or in patients in whom an additional cardiopulmonary insult might be deadly (such as a patient with acute respiratory distress syndrome and a DVT). Reports of safely extracting VCI devices up to a year after placement have been published, although more commonly retrieval occurs within several months of placement (or not at all). In patients with a VCI in place, one should take extra care with placement of central venous catheters (CVCs), as the guide wire from longer CVCs can engage and displace these devices.

DURATION OF THERAPY

Although often not a decision firmly made in the ICU, any practitioner caring for a patient with VTE should consider the duration of anticoagulation. Duration of therapy remains one of the more controversial aspects to the treatment of DVT and PE, and thinking has evolved from a pure time-based decision to an incorporation of the patient's risk for and personal history with VTE. A distinction is made between patients with "secondary" VTE, in whom a temporary risk factor such as surgery, trauma, endothelial damage, or temporary immobility (casting) is identified, and patients with apparent "idiopathic" VTE occurring unpredictably. When a reversible risk factor such as surgery can be identified prior to an initial proximal DVT, most authors would recommend a 3-month course of anticoagulation (typically with oral warfarin) and then discontinuation, assuming that the risk factor is no longer present. When a proximal DVT occurs in the absence of an identifiable risk factor, as the second occurrence of VTE, or in a patient with ongoing risk for VTE (e.g., cancer or an inherited thrombophilia), it is recommended that, after 3 months of initial anticoagulation, a risk-benefit assessment for indefinite anticoagulation be made, with lifelong anticoagulation the preferred treatment unless the risk of bleeding is deemed too great. For highly symptomatic or life-threatening PE, the same recommendations apply, except that the initial duration of therapy may be extended to 6 to 9 months even in patients in whom an identifiable risk factor is present. Lifelong anticoagulation is recommended for any patient whose PE prompts admission to the ICU unless the patient is deemed to be at very high risk for anticoagulation or the patient's single risk factor is definitely reversed (e.g., cancer-free for > 1 year). Some use clot resolution by either repeat venous ultrasonography or pulmonary CTA to guide therapy duration, but this practice may underestimate ongoing risk factors for forming new clots, and insufficient evidence exists to recommend the practice at this time.

An annotated bibliography can be found at www.expertconsult.com.

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Wells PS, Anderson DR, Stiell RM, et al: Excluding pulmonary embolism at the bedside without diagnostic imaging: managment of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. Ann Intern Med 135:98-107, 2001.

This is the classic prospective cohort study that validated the accuracy and usefulness of the Wells criteria (Table 77.1) as risk stratification tool (low, moderate and high risk categories) plus D-dimer in a large population of patients presenting to emergency departments at four tertiary care hospitals in Canada.

CHAPTER 78

Diffuse Alveolar Hemorrhage

Lee Gazourian ■ Maryl Kreider ■ Gerald L. Weinhouse

Diffuse alveolar hemorrhage (DAH) is characterized by the clinical triad of (1) blood in the terminal airspaces, (2) anemia, and (3) infiltrates on chest radiographs. In DAH, bleeding occurs at the level of the alveolar capillaries, arterioles, or venules. Hemoptysis may not occur, as the bleeding is located in these most distal portions of the lung and may be absorbed before expectoration. However, bronchoalveolar lavage (BAL) will still yield erythrocytes and hemosiderin-laden macrophages. Patients with lethal DAH die of refractory hypoxemia and not exsanguination or airway obstruction.

This chapter reviews the clinical presentation of DAH, describes an approach to its diagnosis, and briefly summarizes the management approach to the most common causes of DAH.

Clinical Presentation

Patients typically present with acute to subacute symptoms of dyspnea, cough, and hemoptysis. Any fever at presentation is usually related to the underlying etiology. Absent hemoptysis, these very nonspecific presentation findings require a high degree of clinical suspicion to confirm the diagnosis. Untreated DAH is often life threatening and is associated with a poor prognosis. Consequently, the clinician must maintain a high index of suspicion and work quickly to diagnose DAH, identify the likely etiology, and select an appropriate therapy.

PHYSICAL EXAMINATION

The physical examination is nonspecific but may provide clues to an underling systemic vasculitis, collagen vascular disorder, or cardiac etiology. Physical findings may be indistinguishable from those found in other alveolar filling processes (i.e., pulmonary edema), which may help explain why the diagnosis is initially unexpected in the majority of cases.

RADIOLOGY

The chest radiograph (CXR) in DAH is usually abnormal but nonspecific. Alveolar infiltrates are usually present and diffuse, but they may rarely be focal or asymmetric. The diffuse infiltrates are often indistinguishable from those of pulmonary edema. The computed tomographic (CT) scan of the lung is characterized by a nonspecific alveolar-filling pattern, which may demonstrate areas of consolidation interspersed with areas of ground-glass attenuation and other normal areas. A CT scan may be useful diagnostically in detecting ground-glass opacities when DAH is suspected in the presence of a normal CXR. However, once DAH is suspected with an abnormal CXR, CT rarely offers additional benefit.

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LABORATORY EVALUATION

Initial screening tests should include a complete blood count including platelet count, prothrombin and partial thromboplastin times, blood urea nitrogen and creatinine determinations, and urinalysis including the urine sediment. An admission electrocardiogram may reveal occult cardiac disease and provide a baseline in the event that hemodynamic compromise with cardiac injury ensues. Finally, sputum, if available, should be sent for Gram stain and culture.

Serologic studies are an important diagnostic tool in DAH. However, their results often are unavailable for several days, so they often do not contribute to the acute management of the patient. *Antinuclear antibody* (ANA) and *anti–double-stranded DNA* support the diagnosis of systemic lupus erythematosus (SLE). However, a small percentage of patients with SLE are seronegative. If a pulmonary-renal syndrome is suspected, titers of both *antiglomerular basement membrane antibody (anti-GBM)* and *antineutrophil cytoplasmic antibody (ANCA)* should be sent. A high titer of anti-GBM supports the diagnosis of Goodpasture syndrome. ANCA titers are reported as either cytoplasmic (C-ANCA) or perinuclear (P-ANCA). A high C-ANCA titer with a positive enzyme-linked immunosorbent assay (ELISA) for antibody to proteinase 3 (PR3) is highly specific and sensitive for granulomatosis with polyangiitis (GWP, historically known as Wegener's granulomatosis). A high P-ANCA titer with a positive ELISA for antibody to myeloperoxidase (MPO) is associated with several small-vessel vasculitides, including microscopic angiitis (which can cause DAH) as well as Churg-Strauss syndrome and, rarely, some drug reactions. Many other disorders, including infections, can result in positive C-ANCA or P-ANCA, emphasizing the need to test for antibody to PR3 or MPO by ELISA.

Significant obstruction or restriction from pulmonary function testing could suggest an underlying lung disease that may be leading to the hemorrhage. The diffusing capacity (DLco) is frequently touted as a way to diagnose pulmonary hemorrhage. The red blood cells in the air spaces absorb the carbon monoxide administered during the test, leading to an elevation in the DLco. However, patients with DAH in the ICU are rarely stable enough for pulmonary function testing to be practical.

BRONCHOSCOPY

Bronchoscopy with bronchoalveolar lavage (BAL) should confirm DAH by documenting an increasing red blood cell count in serial aliquots from the same location. In addition, bronchoscopy aids in the exclusion of an associated infectious process and specimens of the BAL should be sent for bacterial, fungal, and viral cultures, as well as *Pneumocystis jiroveci (carinii)* when clinically indicated.

It has been suggested that ≥ 20% hemosiderin-laden macrophages in BAL is diagnostic of DAH. However, these findings vary according to the timing of the bronchoscopy in relation to the onset of bleeding. Increasingly bloody BAL returns are most sensitive and specific in the first 48 hours of bleeding before spillage can occur, and it takes 48 hours for macrophages to become hemosiderin laden. In addition, hemosiderin-laden macrophages can be found in patients with biopsy-proven diffuse alveolar damage, without DAH.

SURGICAL LUNG BIOPSY

Surgical biopsy may be warranted when serologic workup fails to provide a diagnosis. Likewise, if a patient is deteriorating and the serology is pending, biopsy should also be considered. Empiric therapy often begins before establishing a diagnosis in patients admitted to the ICU because of DAH; however, the diagnosis of the underlying etiology (and exclusion of unsuspected other diagnoses) will ultimately be necessary to determine the duration and intensity of immunosuppression.

Open lung biopsy or the less invasive video-assisted thoracoscopic surgery (VATS) is the preferred means of biopsy. The yield of transbronchial biopsies is limited by sampling error and the

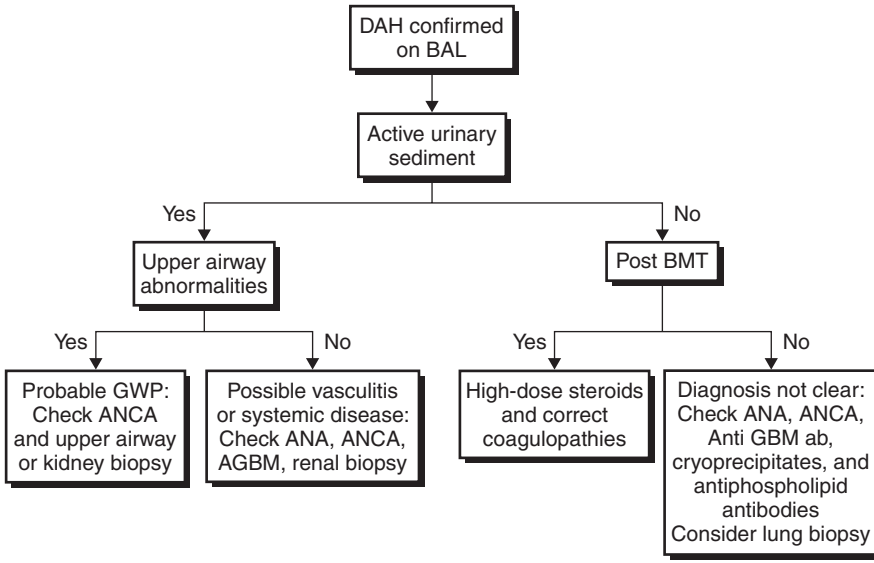


Figure 78.1 Evaluation of diffuse alveolar hemorrhage.

small amount of tissue obtained by this procedure. Lastly, if a pulmonary-renal syndrome, such as Goodpasture syndrome, is suspected, one should consider renal biopsy to establish the diagnosis.

SECONDARY (INTEGRATED) DIAGNOSTIC WORKUP (FIGURE 78.1)

Once the diagnosis of DAH has been established with BAL and concomitant infection ruled out, a more detailed medical and exposure history should be taken to look for evidence of collagen vascular disease, vasculitis, and toxin/drug exposure. A urinary sediment should be examined for evidence of renal involvement. If there is renal involvement, appropriate serologies including ANA, anti-GBM, and ANCA should be sent. If there are symptoms or evidence of sinus disease in addition to evidence of renal involvement so that there is a high suspicion for GWP, a sinus biopsy should be considered; otherwise, a kidney biopsy is typically preferred to confirm the diagnosis. For the critically ill patient with a clinical story compelling for any of the pulmonary renal syndromes, treatment with high-dose steroids can begin while awaiting the tests results, as most of these syndromes are treated similarly (discussed later).

Absent evidence of kidney involvement by urinalysis and serum creatinine, then the same serologies should still be sent. In addition, one should send the patient's blood for an antiphospholipid antibody, cryoglobulins, and hepatitis B serologies. If all of these are unrevealing, surgical lung biopsy may be necessary, although some patients may be too ill or unstable for biopsy. The major advantage of a biopsy is a more confident diagnosis in the future when considering ongoing cytotoxic therapy.

One exception to this evaluation is a patient who has had a stem cell transplant. If BAL confirms DAH and excludes infection, consider empiric therapy without additional testing.

Differential Diagnosis of DAH

The causes of DAH may be categorized into three groups based on histologic findings: (1) those with vasculitis or capillaritis present, (2) those with no associated vasculitis or capillaritis

TABLE 78.1 ■ **Etiologies of Diffuse Alveolar Hemorrhage Categorized by Histologic Appearance**

Capillaritis	Bland	Secondary
ANCA Associated	Drugs	Diffuse alveolar damage
GWP	—Anticoagulants	Pulmonary embolus
Microscopic polyangiitis	—Phenytoin	Sarcoidosis
Churg-Strauss syndrome	—Penicillamine	High altitude pulmonary edema
Essential mixed cryoglobulinemia	—Mitomycin	Barotrauma
Behçet's syndrome	—Nitrofurantoin	Infection
Henoch-Schönlein purpura	—Cocaine	Invasive aspergillosis, CMV, legionella, hantavirus, leptospirosis
IgA nephropathy	—Amiodarone	Post-BMT
Immunologic	—Pesticides	Malignancies in the lung
Goodpasture syndrome	Mitral stenosis and mitral regurgitation	Lymphangioleiomyomatosis
Connective tissue disorder	Pulmonary veno-occlusive disease	Pulmonary capillary hemangiomatosis
Acute lung rejection	Infection	
Antiphospholipid antibody syndrome	HIV, endocarditis	
Cryoglobulinemia	Toxins	
Isolated Pauci–Immune	Isocyanates, trimellitic anhydride, pesticides, detergents	
Pulmonary capillaritis	Idiopathic pulmonary hemosiderosis	
Drug induced	Coagulation disorders	
Propylthiouracil		
All-trans retinoic acid		
Diphenylhydantoin		
Thrombocytopenias		
Idiopathic thrombocytopenic purpura		
Thrombotic thrombocytopenic purpura		

ANCA, Anti-neutrophil cytoplasmic autoantibody; GWP, granulomas with polyangiitis.

("bland hemorrhage"), and (3) those associated with another process or condition. Typical changes seen in capillaritis include fibrin thrombi occluding the capillaries of the alveolar septae, fibrinoid necrosis of the capillary walls, and perivascular and interstitial accumulation of fragmented neutrophils with an associated extravasation of red blood cells into the alveoli and interstitium. In bland hemorrhage there is extravasation of the red blood cells without any accompanying inflammation or destruction of the capillaries, venules, or arterioles. Finally, the extravasation can occur in the setting of another lung pathology such as diffuse alveolar damage, metastatic tumor, lymphangioleiomyomatosis, sarcoidosis, or other disorders.

Table 78.1 illustrates the multiple etiologies that should be considered when evaluating a patient with DAH.

Treatment of Diffuse Alveolar Hemorrhage

Systemic immunosuppression is the cornerstone of therapy for almost all forms of DAH. High-dose corticosteroids (either methylprednisolone at 500 to 1000 mg/day intravenously or prednisone at 1 to 2 mg/kg/day depending on the gravity of illness) are frequently initiated early on, even when the diagnosis is unclear and in particular if there is evidence to support a vasculitis or other systemic disease.

CAPILLARITIS

Granulomatosis with Polyangiitis (GWP)

The triad of sinusitis, glomerulonephritis, and lower respiratory tract disease should prompt immediate concern for GWP. However, the clinical appearance of the disease sometimes is limited to the respiratory tract (limited form of GWP). Life-threatening DAH as a result of a necrotizing vasculitis may be the presenting sign, but it is not the most common pulmonary presentation of the disease. Other organs including eyes and skin can be involved. As noted earlier, GWP is most commonly associated with a positive C-ANCA, with increased sensitivity and specificity from a positive PR3. Lung biopsy is generally nondiagnostic in patients with GWP who present with DAH; these patients often do not have the typical masslike lesions of GWP (granulomas) evident on their chest radiographic studies, including chest CT scans.

Microscopic Polyangiitis

This small vessel vasculitis can lead to DAH from pulmonary capillaritis (in 10% to 30% of patients), although it most frequently has kidney involvement (80% to 100% of patients) and at times skin and joint manifestations. Microscopic polyangiitis is typically associated with a positive P-ANCA with associated antibody to MPO.

Isolated Pulmonary Capillaritis

This condition is another small vessel vasculitis that appears similar to microscopic polyangiitis but is limited to the lung without kidney involvement. Again, P-ANCA staining may be present but patients are often ANCA negative and the diagnosis can only be made by lung biopsy.

Goodpasture Syndrome

Glomerulonephritis associated with anti-GBM may present with pulmonary hemorrhage in classic Goodpasture syndrome. However, the pulmonary manifestations may precede the renal disease by months. Diffuse autoimmune vascular injury produces pulmonary bleeding. Serum antibodies are detected in > 90% of affected patients. Renal biopsy, not open lung biopsy, is the preferred diagnostic approach. In Goodpasture syndrome, renal biopsy reveals the characteristic linear, immunofluorescent staining pattern of glomeruli, whereas a lung biopsy may show only nonspecific staining.

Collagen Vascular Diseases

SLE and systemic sclerosis are the collagen vascular diseases most commonly associated with DAH. However, there are reports of DAH in rheumatoid arthritis, polymyositis, and mixed connective tissue disease as well.

Although pulmonary involvement by SLE is relatively common, DAH is uncommon (approximately 2%). It is unusual for DAH to be the first manifestation of SLE, and most patients have active nephritis concomitantly. Nonetheless, the diagnosis of SLE should be considered in any patient with DAH. Tissue examination will reveal an immune complex vasculitis, with granular deposition of immunoglobulin and complement in the alveolar interstitium and small vessels.

BLAND HEMORRHAGE

Bone Marrow Transplantation (BMT)

DAH is a common complication of BMT (studies range from 2% to 39%). Concomitant infection is frequent (40%), though no one infection or even type of infection is consistently found. DAH is more common after autologous than allogeneic BMT, but can occur in either patient population. Risk factors include age > 40 years, total body irradiation, transplantation for solid tumors, high fever, and renal insufficiency.

The time course from transplant varies with most cases occurring 10 to 40 days after transplant with a wide reported range of 0 to 105 days. Direct induction regimen toxicity, an enhanced inflammatory response in the airways, and coexistent coagulopathy all appear to play a role. The DAH in BMT seems to respond to systemic corticosteroid therapy in some patients. Patients with autologous BMT and early onset of DAH tend to have a more favorable prognosis, yet mortality remains high with most studies suggesting a > 50% mortality for patients requiring mechanical ventilation.

Idiopathic Pulmonary Hemosiderosis

Idiopathic pulmonary hemosiderosis is a rare disorder of recurrent (and at times acute life-threatening) DAH. It typically presents in children but can occur in young adults. Some cases appear associated with celiac disease and other cases with exposures to certain molds including *Stachybotrys atra*. The diagnosis is made by exclusion of other causes of DAH.

Drug-Associated DAH

Many different drugs have been implicated in the development of DAH and may be associated with capillaritis or a bland pathology. Some, such as diphenylhydantoin, all-trans retinoic acid, and propylthiouracil have been associated with the development of capillaritis. Anticoagulants can contribute to a bland DAH. Some drug toxicities that lead to diffuse alveolar damage can lead to DAH indirectly. For most of these etiologies of DAH, cessation of the inciting drug may be sufficient to treat the condition. Drug-induced DAH cases associated with capillaritis may also need anti-inflammatory therapy to resolve the accompanying inflammation.

Cyclophosphamide is frequently added. The data for the latter's efficacy are strongest for GWP in which studies from the NIH showed steroids plus cyclophosphamide superior to steroids alone in attaining remission.

Plasmapheresis is of additive benefit if the DAH is secondary to Goodpasture syndrome. Plasmapheresis is often used in other settings, when the titer of either immunoglobulins or immune complexes is high, despite limited supporting data.

DAH after stem cell transplant is also typically treated with high-dose steroids, based on two retrospective case series suggesting that patients treated with high-dose steroids needed less mechanical ventilation and had improved survival. Despite this limited evidence, high-dose steroid therapy for DAH after BMT has become commonplace.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 79

Massive Hemoptysis

Edmund K. Moon ■ Andrew R. Haas

Massive hemoptysis (approximately 5% of all hemoptysis cases) is variably defined as the expectoration of blood greater than 100 to 500 mL over a 24-hour period. It is a medical emergency and often a sign of a serious underlying medical condition. With a mortality rate as high as 75%, death is due to acute airway obstruction and hypoxemic respiratory failure, not exsanguination. With total airway dead space measuring only 150 mL, conducting airways can become obstructed with minimal bleeding if a patient cannot clear blood from his or her tracheobronchial tree.

Anatomy

The lungs have a dual blood supply: the pulmonary arterial circulation participates in gas exchange, while the bronchial arterial circulation supplies the pulmonary parenchyma. The pulmonary arteries branch into lobar arteries and eventually form the fine alveolar capillary interface for gas exchange. The pulmonary arterial circulation is a low-pressure, low-resistance system with capacity to accommodate significant increases in blood flow without a marked pressure increase. The pulmonary parenchyma nutrient supply is provided by the bronchial arteries, which arise from either the aorta or intercostal arteries. In contrast to the pulmonary arterial circulation, the bronchial artery circulation is a high-pressure system with frequent anastomoses that surround the airway and lie in the peribronchial space, and small penetrating arteries that supply the bronchial mucosa via a submucosal plexus. Because of the pressure difference between these two systems, massive hemoptysis is more likely to originate from the bronchial than the pulmonary arterial circulation. Furthermore, in many of the inflammatory and infectious conditions mentioned later, parasitized intercostal arteries can form and become the bleeding source.

Differential Diagnosis of Massive Hemoptysis

Historically, tuberculosis (TB), bronchiectasis, and lung abscess were the most common causes of massive hemoptysis and accounted for approximately 90% of cases. However, the etiologic spectrum has evolved with widespread antibiotic use significantly reducing the infectious disease prevalence causing massive hemoptysis. When a patient presents with massive hemoptysis, recall the phrase "These things INCITE bleeding" as a mnemonic for the differential diagnosis: I – Infection, N – Neoplasm, C – Cardiovascular, I – Iatrogenic, T – Trauma, E – Everything else.

INFECTIONS

Prior to antituberculous medical therapy, TB and its sequelae were the most common cause of massive hemoptysis through various mechanisms: (1) active cavitary disease eroding into adjacent vessels, (2) Rasmussen's (pulmonary artery) aneurysm eroding into an adjacent cavity, (3) residual bronchiectasis from a prior infection, (4) erosion of a broncholith through a vessel into an airway, and (5) mycetoma formation in a prior cavity.

Bronchiectasis is characterized by abnormal bronchial wall thickening with luminal dilatation that manifests clinically as daily cough with sputum production and airflow obstruction (see Box 79.1 for list of causes). Repeated bacterial infections, particularly with *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and chronic airway inflammation are bronchiectasis hallmarks that can lead to enlarged and tortuous bronchial arteries, systemic-pulmonary vascular anastomoses, or parasitized intercostal arteries. Rupture of these vessels can cause rapidly fatal massive hemoptysis.

Fungal infections have become an increasingly common source of massive hemoptysis, particularly in two patient populations: those with preexisting cavitary lung disease and profoundly immunocompromised patients (e.g., hematopoietic stem cell transplantation). Patients with cavitary lung disease can develop intracavitary fungal colonization and mycetoma formation (e.g., aspergilloma). The bronchial and intercostal artery dilation and hypertrophy surrounding these cavities can be dramatic. From 50% to 90% of these patients can have hemoptysis at some course during their disease.

BOX 79.1 ■ Massive Hemoptysis Etiologies

- Infection
  - Tuberculosis/mycobacterial infection
  - Bronchiectasis
  - Fungal infections (primary or mycetoma)
  - Lung abscess
  - Paragonimiasis
  - Hydatid cyst
- Necrotizing pneumonia
- Neoplasm
  - Lung cancer (non-small or small cell)
- Pulmonary carcinoid
- Endobronchial metastases
- Parenchymal metastases
- Cardiac/vascular
  - Arteriovenous malformation
  - Mitral stenosis
  - Pulmonary embolism/infarct
  - Congenital heart defects
  - Pulmonary hypertension
  - Aortic aneurysm
  - Bronchoarterial fistula
- Congestive heart failure (systolic or diastolic)
- Septic emboli
- Iatrogenic
  - Bronchoscopy
  - Transthoracic needle aspiration
  - Pulmonary artery catheterization
  - Tracheo-innominate artery fistula
- Radiotherapy
  - Directed chemotherapeutic agents (e.g., bevacizumab)
- Trauma
  - Blunt chest trauma
  - Penetrating chest trauma
- Everything else
  - Pseudohemoptysis
  - Immunologic lung disease (diffuse alveolar hemorrhage [DAH]; see Chapter 78)
  - Bone marrow transplantation

Interestingly, massive hemoptysis tends to be uncommon in cases of immunocompromised invasive fungal infections until neutrophil count recovery begins after a prolonged neutropenic period.

Other pulmonary infections can cause massive hemoptysis. Lung abscesses caused by polymicrobial and anaerobic bacteria or necrotizing pneumonias caused by *Staphylococcus* species, *Klebsiella pneumoniae*, or *Legionella pneumoniae* can cause massive hemoptysis. Community-acquired methicillin-resistant *S. aureus* has been a source of massive hemoptysis resulting from its tendency to cause both parenchymal cavitation and necrosis.

NEOPLASMS

Any type of bronchogenic carcinoma can cause hemoptysis, which can occur either at presentation (7% to 10 % of cases) or subsequently during the malignancy course (20% of cases). In a large retrospective analysis of more than 800 cases of lung cancer, squamous cell histology was the most frequent cell type associated with massive hemoptysis, followed by adenocarcinoma, small cell carcinoma, and large cell carcinoma. Endobronchial location or cavitation was associated with a higher hemoptysis incidence. New targeted, chemotherapeutic agents (e.g., bevacizumab) with dramatic cavitary responses can predispose to massive hemoptysis.

Any endobronchial or intraparenchymal metastatic tumor to the lung can cause massive hemoptysis. Melanoma, lung, colon, breast, or prostate cancer tends to form endobronchial metastases, whereas renal cell carcinoma, thyroid cancer, and sarcomas tend to form parenchymal metastases that are prone to cause massive hemoptysis.

CARDIOVASCULAR DISEASE

Among the primary cardiac hemoptysis sources (see Box 79.1), elevated pulmonary venous pressure leads to venous dilation and varix formation, which may rupture and bleed during sudden pulmonary venous pressure increases (e.g., systolic or diastolic failure, cough, Valsalva). Such hemoptysis is generally self-limited but can be severe and life threatening on occasion.

IATROGENIC CAUSES

Hemoptysis can complicate a number of invasive procedures. Massive hemoptysis during bronchoscopy is rare and usually occurs in the setting of platelet dysfunction, thrombocytopenia, or coagulopathy. Pulmonary artery catheter flotation causing pulmonary artery rupture has a mortality rate greater than 50%. Avoiding distal migration of the catheter tip and balloon overinflation while ensuring balloon deflation prior to catheter advancement can help avoid this potentially lethal complication.

A tracheal-innominate artery fistula (TIF) may develop in the chronic tracheostomy patient. A low tracheal insertion (below the recommended first to third tracheal rings) or a high innominate artery may lead to erosion and TIF formation. One potential clue to TIF is the "sentinel bleed"—a small amount of fresh tracheal blood that usually appears 2 weeks or more after tracheostomy placement and can portend a catastrophic, fatal bleed.

Massive hemoptysis is a known thoracic radiotherapy complication that more commonly occurs with endobronchial brachytherapy than external beam radiotherapy. Bleeding usually occurs from bronchial necrosis and vascular erosion.

TRAUMA

Rarely, massive hemoptysis may occur following chest trauma. Blunt trauma can cause airway rupture with associated injury to the pulmonary or bronchial vasculature. Alternatively, fractured ribs can cause a lung laceration with hemoptysis, hemothorax, or both. Similarly, penetrating

trauma can directly lacerate the pulmonary, bronchial, or other major vascular structures causing hemoptysis or hemothorax.

EVERYTHING ELSE

Always consider "pseudohemoptysis," or bleeding from a source other than the lung. Epistaxis or hematemesis can mimic hemoptysis, and patients may be unable to differentiate the bleeding source. If pseudohemoptysis is suspected, involving an otolaryngologist or gastroenterologist in the patient's care can be crucial.

Diffuse alveolar hemorrhage (DAH) should always be considered when a patient presents with massive hemoptysis. Interestingly, patients with DAH can have profound hypoxemic respiratory failure with little to no hemoptysis. Box 79.1 details many of the underlying etiologies of DAH, but this topic is addressed in detail in Chapter 78.

Diagnostic Approach

HISTORY AND PHYSICAL EXAM

The basic history and physical exam provide important initial clues to the etiology of massive hemoptysis. Physicians should elicit any recent history of infectious symptoms. Particular attention should focus on prior underlying lung or cardiac disease, occupational or tobacco exposures, or any familial lung or bleeding disorders.

In examining the stable patient, note the presence of any signs of consolidation, abscess, or infarct on examination that might indicate laterality of the massive hemoptysis source. Evidence of congestive heart failure or a malignancy can guide diagnostic evaluation and guide how quickly the patient requires definitive management.

LABORATORY STUDIES

Initial tests should include a complete blood count, coagulation studies, blood urea nitrogen, creatinine, and urinalysis, which may provide clues to the presence of any underlying systemic disorders. Serologies can evaluate for a suspected pulmonary-renal syndrome. Sputum and blood cultures can identify pathogenic organisms when suspecting an infectious source.

RADIOGRAPHIC STUDIES

Radiographic studies form the diagnostic evaluation backbone in massive hemoptysis. A guiding principle is to localize a potentially causative lesion for intervention. The standard chest radiograph can initially identify cavitary lesions, tumors, lobar or alveolar infiltrates, infarcts, or mediastinal masses. However, the false-negative rate of the standard chest radiograph ranges from 20% to 40% in massive hemoptysis.

Computed tomography (CT) scan has greatly enhanced sensitivity compared to a chest radiograph. Contrast enhancement (i.e., CT angiography) can detect pulmonary emboli, arteriovenous malformations, or aneurysms. Moreover, multifocal CT scan abnormalities may help identify bleeding laterality. Two major limitations to CT scan are (1) the time required to obtain the study and (2) supine positioning, which can impair airway clearance in the event of ongoing bleeding. Therefore, in rapidly progressive, life-threatening hemoptysis, bronchoscopic examination should not be delayed by CT studies.

The bronchoscope is an important tool in the diagnosis and management of massive hemoptysis. The flexible bronchoscope is often utilized because of its availability, accessibility, and

physician comfort but can be limited by its minimal suction capacity. The rigid bronchoscope allows simultaneous large bore suction, airway maintenance, and ventilation and is therefore preferred in life-threatening hemoptysis. However, rigid bronchoscopy is limited by physician experience and the equipment setup delay. Unlike the flexible bronchoscope, which can reach the upper lobes and lesions located as far as the sixth bronchial generation, the rigid bronchoscope cannot visualize beyond the trachea and mainstem bronchi. Consequently, the two modalities are often combined to achieve optimal bleeding evaluation and control.

Management

Management of massive hemoptysis and the use of particular therapeutic modalities are influenced by both the underlying etiology and local expertise and resources. Management should be multidisciplinary in nature, involving pulmonary/critical care physicians, cardiothoracic surgeons, and interventional radiologists.

ACUTE MANAGEMENT

The therapeutic cornerstones to massive hemoptysis are assuring a secure airway and attempting to isolate the bleeding source laterality. Because the optimal airway clearance mechanism in the setting of active bleeding is the patient's own cough reflex, endotracheal intubation should *not* be an automatic first reaction to massive hemoptysis. Allowing the patient to clear his or her own airway is more effective than any mechanical intervention. Patients should be monitored very closely in an intensive care unit (ICU). Endotracheal intubation should proceed if a patient cannot clear the bleeding or develops progressive respiratory distress or hypoxemia. Intubation with large-bore endotracheal tubes (e.g., 8.5 or 9 mm internal diameter) is recommended to facilitate suctioning and bronchoscope insertion. Alternatively, the patient could proceed directly to rigid bronchoscopy, to allow simultaneous large volume suctioning, ventilation, and photocoagulation modalities if needed.

The second management cornerstone is ascertaining bleeding source laterality (i.e., to isolate the bleeding site). Blood spillage into the unaffected, normal lung can either obstruct the airway with clot or prevent alveolar gas exchange. Therefore, preventing the spread of blood to the uninvolved lung in unilateral hemoptysis is a priority. The initial method to accomplish this goal is to place the patient in the lateral decubitus position with the bleeding source lung down, thereby minimizing blood flowing into the uninvolved lung.

Once the decision for endotracheal intubation is made, physicians should be prepared to provide airway clearance, as all natural airway protective mechanisms are obliterated upon endotracheal intubation. Initially, selective lung intubation should occur to isolate the uninvolved lung from continued bleeding. The endotracheal tube should be advanced far enough to allow endotracheal balloon inflation in the mainstem bronchus to prevent further blood from entering the uninvolved lung. If available, selective lung intubation with direct bronchoscopic visualization is technically easier.

Two other mechanical approaches to isolate bleeding involve using balloon occlusion devices. Upon intubation, bronchoscopy can determine the bleeding source and a Fogarty embolectomy balloon can be passed through the bronchoscope and inflated to occlude the airway. This technique is only a temporizing measure, as the bronchoscope cannot remain in the endotracheal tube for a prolonged time period. However, occlusion of the bleeding airway may allow enough time for clot formation and hemostasis. In contrast, a bronchial blocker can remain fixed in place for a prolonged time period. A specialized endotracheal tube adaptor allows for bronchial blocker insertion and fixation through a separate port from the ventilation port. The bronchial blocker has three limitations: (1) bronchial blocker availability, (2) pediatric bronchoscope availability, and (3) technical

insertion prowess. The bronchial blocker balloon occlusion method is also a temporizing measure prior to a definitive procedure.

Finally, double lumen endotracheal tube intubation allows independent lung ventilation and toileting, but accurate tube placement can be difficult and time consuming. Limitations such as narrow lumen diameter predisposed to blockage, the need for specialized suction catheters, and neuromuscular paralysis have limited the use of double lumen tubes in massive hemoptysis management.

Anecdotal data support iced saline lavage, topical epinephrine, vasopressin, thrombin, or a fibrinogen-thrombin composite attempt via the bronchoscope to create vasoconstriction and hemostasis. Laser therapy, electrocautery, or cryotherapy can also be performed if a bleeding mucosal lesion is visualized during bronchoscopic examination. Other measures reported include placement of endobronchial blockers or temporary surgical packing (i.e., absorbable hemostatic fabric or spongelike material) into bleeding airways to create hemostasis while more definitive measures are considered.

If a TIF is suspected, immediate cardiothoracic surgery or otorhinolaryngology consultation must be initiated. Until surgical repair is under way, a few temporizing maneuvers can be performed to tamponade the arterial lesion: (1) tracheostomy tube cuff hyperinflation and (2) tracheostomy tube exchange with standard oral endotracheal intubation, followed by finger insertion into the tracheostomy stoma applying anterior pressure against the sternum to tamponade bleeding.

DEFINITIVE TREATMENT

Bronchial artery embolization (BAE) was first performed in the 1970s and has become the most utilized nonsurgical treatment modality because of both short-term (over 90%) and long-term (over 80%) effectiveness. Successful embolization depends largely on the ability to delineate the vascular anatomy angiographically. In patients with recurrent bleeding despite embolization (10% to 20% over 6 to 12 months), repeat embolization can be attempted. Late rebleeding (past 1 year) is usually due to neovascularization or recanalization. BAE complications are uncommon in experienced hands, but bronchial wall necrosis and ischemic myelopathy from inadvertent spinal artery embolization can occur.

Patients with lateralized, uncontrolled bleeding should be assessed early for possible surgery in case the bleeding proves refractory to temporizing measures or BAE. Surgical intervention is usually the treatment choice in massive hemoptysis because of leaking aortic aneurysms, hydatid cysts, iatrogenic pulmonary vascular ruptures, and chest trauma. However, surgery is contraindicated in carcinomatous invasion of the trachea, mediastinum, heart, and great vessels and in advanced lung fibrosis. The surgical mortality rate in massive hemoptysis (defined as death within 7 days postoperatively) ranges from 1% to 50% with emergent cases having the highest mortality rate. Common surgical complications include empyema, bronchopleural fistula, postoperative pulmonary hemorrhage, prolonged respiratory failure, wound infection, and hemothorax. Some centers have reduced mortality by avoiding surgical intervention within 48 hours from hemoptysis onset if bleeding can be temporized with less invasive measures.

Summary

Massive hemoptysis is an uncommon complication of a variety of systemic and pulmonary diseases. Early measures to protect the unaffected lung (when a unilateral source can be identified) as well as temporizing measures to achieve hemostasis should be considered while more definitive treatments with BAE or surgical intervention are evaluated. Expeditious and aggressive multidisciplinary management of these patients often can control bleeding and lead to better patient outcomes.

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CHAPTER 80

Obesity Hypoventilation Syndrome and Other Sleep-Related Breathing Disorders

Bernie Sunwoo ■ Nirav P. Patel† ■ Aharon Sareli ■ Richard J. Schwab

Obesity hypoventilation syndrome (OHS) falls on the severe end of the spectrum of sleep-related breathing disorders (SRBDs) (Table 80.1). Because obesity is a leading risk factor for SRBDs, as the prevalence of obesity and morbid obesity increases, patients with SRBDs, including obstructive sleep apnea (OSA) and OHS, are increasingly admitted to intensive care units (ICUs).

It is not fully understood why some patients move along this continuum to develop the more severe SRBDs and hypercapnia and some with the same rate of weight gain or degree of obesity do not. Nonetheless, physicians need to be aware of the physiologic derangements and ICU complications associated with morbid obesity (Chapter 29), including SRBDs such as OHS.

OHS is associated with significant morbidity and mortality, high health care resource utilization, and increased likelihood of ICU admissions, often presenting with acute or chronic hypercapnic respiratory failure. Furthermore, it has been shown that sleep-disordered breathing may affect length of stay and complications in the ICU. Consequently, early identification of OHS and other SRBDs in ICU patients is essential to initiating appropriate treatment. This chapter presents the pathophysiologic features of OSA, central sleep apneas (CSAs), and OHS, and a diagnostic and management strategy for these conditions in the ICU.

Obstructive Sleep Apneas (OSAs)

Obstructive sleep apnea (OSA), a condition of upper airway instability, is present when there are repetitive episodes of cessation of respiration (apnea), decrements in airflow (hypopnea), or both during sleep, associated with sleep fragmentation, arousals, and reductions in oxygen saturation. An apnea (defined as no flow for > 10 seconds) can be obstructive, central, or mixed (i.e., both obstructive and central). A hypopnea is commonly defined as a decrement in airflow of 50% or more for 10 seconds associated with a 4% fall in oxygen saturation or electroencephalographic (EEG) arousal. However, the exact definition of a hypopnea remains debated.

The diagnosis of OSA is most often made in the outpatient setting following an in-laboratory polysomnogram, although this may change with the expansion of coverage for portable, unattended, in-home sleep studies. The apnea/hypopnea index (AHI, referring to the number of apneas plus hypopneas per hour of sleep) is the standard metric used to quantify the severity of obstructive sleep apnea. Although there is no consensus definition of OSA, an AHI > 5 events/hour with associated symptoms (or 15 or greater regardless of associated symptoms) is typically used to define OSA.

Clinical features suggestive of OSA include snoring, snorting or gasping, witnessed apnea, and daytime somnolence. Patients typically have large neck circumference measurements

†Deceased.

TABLE 80.1 ■ **Spectrum of Sleep-Related Breathing Disorders**

Degree of Severity	Form	Comment
Mild	Snoring	Worsens with alcohol.
	Respiratory effort related arousal (RERA)	Episode of increasing respiratory effort or reduced airflow ≥ 10 sec leading to arousals* that do not meet criteria for hypopnea or apnea.†
	Hypopnea	Episode of decreased airflow lasting ≥ 10 sec associated with either a fall in arterial oxygen saturation or arousals.‡ It may be due to partial occlusion of upper airway, decreased central neuronal respiratory drive, or both.
	Apnea	Episode of ≥ 90% decrease in airflow lasting ≥ 10 sec. It may be due to occlusion of upper airway (obstructive), decreased central neuronal respiratory drive (central), or both.
	Obstructive sleep apnea (OSA)	Repetitive apneas, hypopneas, or both during sleep. The apnea hypopnea index (AHI) is the average number of apneas and hypopneas per hour of sleep. An AHI > five events per hour is considered abnormal.
Severe	Obesity hypoventilation syndrome (OHS)	Patients are morbidly obese with evidence of nocturnal hypoventilation and daytime $Paco_2$ elevation while awake.

*Arousals: an electroencephalographically defined change in state from a deeper stage of sleep to a lighter stage of sleep or to wakefulness, often manifested by the presence of alpha activity.
†≥ 5 RERAs per hour and daytime hypersomnolence was previously called upper airway resistance syndrome (UARS).
‡Variable definitions of hypopnea exist that differ in the degree of airflow reduction (30% to 50%) and oxyhemoglobin desaturation (3% to 4%).

(men > 17 inches, woman > 15 inches), macroglossia, elongated or enlarged soft palate, lateral narrowing of the pharynx, tonsillar hypertrophy, retrognathia, and a crowded upper airway (e.g., class 4 modified Mallampati class; Figure 80.1).

Anatomic narrowing of the upper airway is a major factor in the pathogenesis of SBRDs. In addition, a neural component with reduction in the activity of the upper airway dilator muscles, predisposing to upper airway collapse, during sleep is likely involved. Repeated apneic events often result in oxyhemoglobin desaturation, arousals (change in sleep state from a deeper stage of sleep to a higher stage of sleep or wakefulness, often manifested by the presence of an alpha pattern on the electroencephalogram), sleep fragmentation (disruption of the normal sequence of sleep stages and cycling), and sleep deprivation, especially decreased rapid eye movement (REM) sleep.

OSA is a systemic disorder associated with various clinical consequences including systemic hypertension, cerebrovascular disease, arrhythmias, coronary artery disease, congestive heart failure, mild pulmonary hypertension, and insulin resistance. Although patients may report loud snoring, apneas or choking witnessed by bed partners, excessive daytime sleepiness, unrefreshing sleep, nocturia, intellectual impairment, and irritability, a detailed sleep history is often limited in the ICU and a high index of clinical suspicion is necessary. This is particularly true in the obese patient, as obesity is the major risk factor for OSA. Oropharyngeal examination may be helpful in identifying ICU patients with obstructive sleep apnea. Such patients may have a high Mallampati classification—that is, class 3 or 4 during oral cavity examination (see Figure 80.1)—retrognathia, and enlargement of the tongue, lateral peritonsillar tissue, soft palate, and tonsils.

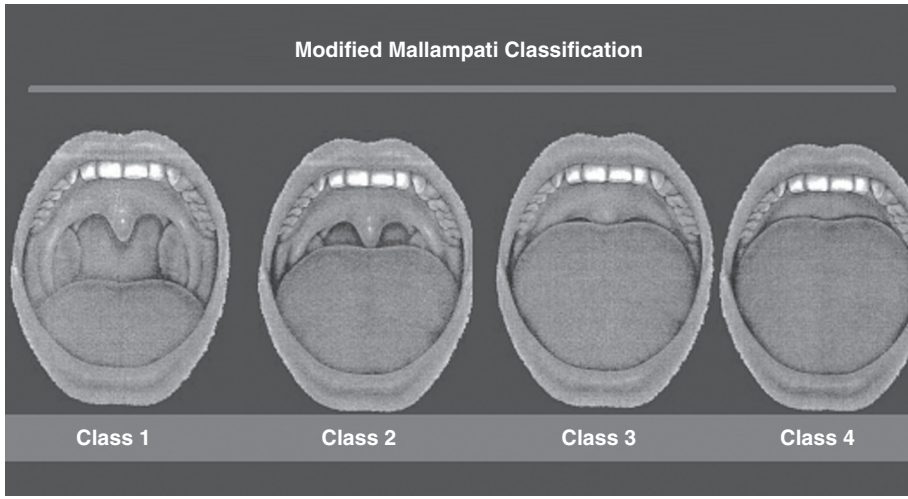


Figure 80.1 Modified Mallampati classification. The patient's oral pharynx is examined in the sitting position with the tongue protruded voluntarily. For class 1, one can see the entire uvula and tonsils; for class 2, one can see the uvula but not the tonsils; for class 3, one can see the proximal soft palate but not the uvula; for class 4, one can see only the hard palate. Most patients with sleep apnea are class 3 or 4. *(From Mallampati SR, Gatt SP, Gugino LD, et al: A clinical sign to predict difficult tracheal intubation: a prospective study. Can Anaesth Soc J 32:429-434, 1985.)*

In inpatients, overnight pulse oximetry and portable sleep testing can assist with the diagnosis of OSA. However, in intubated patients, the assessment for OSA can be challenging. Nonetheless, history (from family) and physical examination combined with an assessment of the airway (typical features stated previously) upon extubation can raise appropriate suspicion. This is important because intubated patients with OSA should be extubated to continuous positive airway pressure (CPAP).

The American Society for Anesthesia has developed a tool for the identification and assessment of OSA in the preoperative period. A significant level of confidence for the diagnosis can be achieved at the bedside by observing sleep-related cyclical oxygen desaturations associated with apnea. First-line treatment of OSA is with CPAP. Pressures can be titrated by observing residual apnea and cyclical desaturations during sleep or by utilizing auto-titrating CPAP units. Of note, third-party payers may require polysomnography-diagnosed OSA to justify coverage of a CPAP apparatus. Therefore, high-risk patients can be discharged from the hospital to the sleep laboratory (for polysomnography) to expedite diagnosis and to initiate treatment.

It is important to identify occult or undiagnosed OSA in the acute setting, because many studies describe significant associations with common medical indications for ICU admission, including atrial fibrillation, stroke, myocardial infarction, hypertension, pulmonary hypertension, and pulmonary edema. Several case reports suggest that OSA is the cause of acute presentations of negative pressure pulmonary edema because of large negative swings in intrathoracic pressure. OSA remains associated with an increase in perioperative morbidity (episodic hypoxemia, sudden respiratory arrest, myocardial ischemia, heart block, and delirium), unplanned ICU transfer, and a prolonged length of ICU stay.

Patients with suspected OSA need careful attention to airway management, as both intubation and extubation may be more challenging. Intubating patients with OSA can be difficult because of a crowded upper airway and may require experienced anesthesiologists or fiberoptic intubation. The timing of extubation should be guided by the patient's alertness, which in turn is influenced

by several factors including sedatives and narcotics. Centrally acting medications—for example, benzodiazepines, anesthetic agents, and narcotics—alter normal responses to hypoxia and hypercapnia and facilitate collapse of the upper airway in OSA patients. At the time of extubation, patients with a history or risk for OSA should have positive airway pressure therapy available. Absent contraindications, routine extubation of OSA patients to CPAP is preferred, although no studies address this issue.

Central Sleep Apneas (CSAs)

Central sleep apnea (CSA) is characterized by repeated episodes of apnea during sleep in the absence of any respiratory effort. The pathogenesis of central sleep apnea is related to a transient loss of central nervous system drive to the respiratory muscles (Chapter 1). In contrast, in OSA, respiratory effort is preserved but airflow is prevented by upper airway occlusion. An overnight polysomnography (which monitors the electroencephalogram, extraocular muscles, airflow at mouth and nose, and movements of the chest wall, abdomen, and extremities) can differentiate central from obstructive apnea, but currently their utility in the ICU remains unknown. CSA, but not OSA, produces the absence of nasal-oral airflow and thoracoabdominal excursion observed on the polysomnogram.

Although CSA can be idiopathic, more commonly CSA in the ICU is due to congestive heart failure where Cheyne-Stokes breathing (a waxing-waning pattern of respiration) may be observed, along with brain stem and neuromuscular disease and opioid use.

Cheyne-Stokes respiration (CSR), a subtype of CSA, represents periodic breathing with alternations between apnea and hyperpnea (Figure 80.2). CSR manifests in patients with severe congestive heart failure (CHF) and stroke, with a cited prevalence in CHF varying widely between 30% and 100%. The primary hypothesized pathophysiology is hyperventilation, producing hypocapnia below the threshold required to trigger breathing.

Importantly, CSR-CSA is associated with worse outcomes in CHF patients. Widespread utilization of beta-blocker therapy for CHF was thought to have reduced the prevalence of CSR, until a prospective study failed to validate this conclusion. As with OSA, a presumptive diagnosis of CSR-CSA can be established with bedside observation of an apnea-hyperpnea cycle lasting at least 45 seconds during sleep or sleep onset. The identification of CSR-CSA often signifies a need to optimize the CHF medical regimen as the primary treatment for CSR-CSA.

However, CPAP, bi-level ventilation (bi-level), and adaptive servo-ventilation (ASV) complement medical therapy. ASV provides servo-controlled, independently varying expiratory and inspiratory pressure support, based on the detection of CSR with a backup respiratory rate. The machine servo-controls the patient's ventilation to achieve a target of 90% of the long-term average ventilation. Studies utilizing ASV in CSR-CSA patients have reduced central events,

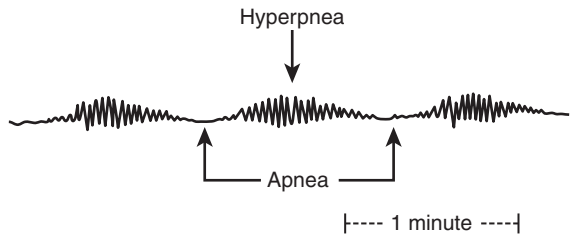


Figure 80.2 Cheyne-Stokes respiration. The Cheyne-Stokes pattern of breathing is characterized by alternating periods of hyperpnea and apnea in a crescendo-decrescendo pattern. Typically, the duration of hyperpnea is longer than that of apneas.

micro-arousals, daytime sleepiness, and improved compliance compared to patients on CPAP or sham ASV. However, to date, no impact of ASV upon cardiovascular outcomes has been proven.

Obesity Hypoventilation Syndrome (OHS)

The definition of OHS is challenging and hampered by differing nomenclature and criteria. The American Academy of Sleep Medicine developed criteria for sleep hypoventilation syndrome, which subsumes OHS, although current literature commonly utilizes the latter term (Table 80.2). In spite of the discrepant definitions and criteria, the well-established phenotype of OHS includes obesity (especially a body mass index [BMI] > 40 kg/m^2 that the CDC defines as morbid obesity) and chronic alveolar hypercapnia (daytime Pco_2 > 45 mm Hg) in the absence of other etiologies of alveolar hypoventilation (such as existing pulmonary and neuromuscular disease). Oxyhemoglobin desaturations detected by nocturnal pulse oximetry can clue the diagnosis in an obese patient (Figure 80.3).

An additional pertinent feature with both pathophysiologic and practical significance to the ICU practitioner is the significant rise in sleeping $Paco_2$ (typically in excess of 10 mm Hg above awake supine values). This nocturnal hypercapnia and concomitant acidemia can be used to identify potential OHS and titrate positive airway pressure during an ICU stay. However, hypercapnia has multiple etiologies, especially in the ICU (including pulmonary disease, neurologic insult, and pharmacotherapy); therefore, a thorough evaluation is necessary prior to asserting a diagnosis of OHS.

In contrast to OHS, patients with OSA do *not* manifest daytime hypercapnia. It is not uncommon for OHS patients to present to the ICU decompensated with acute on chronic hypercapnic respiratory failure, often following an acute illness or the use of sedative medications. In all obese patients with hypercapnic respiratory failure, one should consider OHS in the differential diagnosis.

The risk of OHS increases as obesity increases, with a reported prevalence of almost 50% in hospitalized patients with a BMI greater than 50 kg/m^2. OHS patients are frequently morbidly obese (BMI ≥ 40 kg/m^2). However, the precise mechanism by which morbid obesity leads to hypoventilation remains incompletely understood. A complex interaction between SRBD,

TABLE 80.2 ■ **Diagnostic Criteria for Sleep Hypoventilation Syndrome**

Must Fulfill Both Criteria A and B	
Criteria A (one or more of the following)	***Predisposing Factors***
Cor pulmonale	Morbid obesity (BMI > 35 or > 40)
Pulmonary hypertension	Chest wall restriction disorder
Hypersomnolence	Neuromuscular weakness or disorder
Erythrocytosis	Brain stem or spinal cord lesion
$Paco_2$ > 45 mm Hg while awake	Idiopathic central alveolar hypoventilation
Criteria B (overnight monitoring demonstrates one or both of the following):	Obstructive lung disease
1. An increase in $Paco_2$ during sleep > 10 mm Hg from awake supine values	Hypothyroidism
2. Oxygen desaturation during sleep not explained by apnea or hypopnea events	

Adapted from Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 22:667-689,1999.

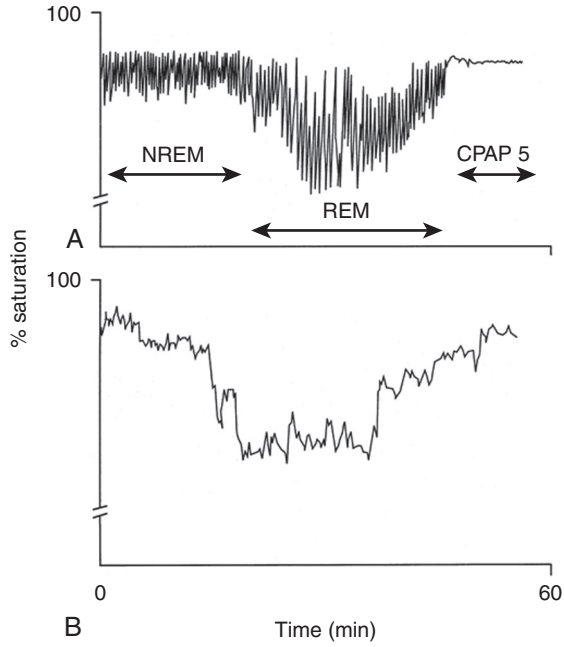


Figure 80.3 Oximetry tracings in OSA and OHS. Panels A and B show characteristic pulse oximetry tracings of a patient with OSA (panel A) and OHS (panel B). The latter demonstrates sustained oxyhemoglobin desaturations secondary to hypoventilation in a patient with OHS. Panel A shows repetitive desaturations that are accentuated during rapid eye movement (REM) and abolished by CPAP, a classic pattern for OSA. Patients with OSA normalize their oxygen levels after each apnea/hypopnea, but patients with OHS show persisted oxyhemoglobin desaturations that do not normalize during sleep.

abnormal respiratory system mechanics resulting from obesity (reduced chest wall and respiratory system compliance, increased airway resistance, expiratory flow limitation, development of intrinsic positive end-expiratory pressure, reduced respiratory muscle efficiency, and increased work of breathing), blunted central respiratory drive, and neurohormonal abnormalities including leptin (an adipokine that stimulates ventilation) resistance likely exist.

OHS patients typically report symptoms of OSA, but additionally symptoms of hypercapnia including morning headaches (secondary to the nocturnal hypercapnia) may be present and help differentiate OHS patients from eucapnic OSA patients. Pulmonary hypertension, cor pulmonale, and polycythemia are more common in patients with OHS compared to patients with OSA. Physical examination may reveal facial plethora, injected sclera (secondary to central nervous system [CNS] vasodilation from hypercapnia), a prominent pulmonic component of the second heart sound and signs of right heart failure including peripheral edema.

Compared to eucapnic OSA patients, OHS patients also commonly have hypoxemia while awake, typically with a PaO_2 < 70 mm Hg. Awake hypoxemia is not common in eucapnic OSA patients and a pulse oximetry recording < 90% should prompt an arterial blood gas (ABG) measurement. A characteristic pattern is often seen on nocturnal oximetry that distinguishes OHS from OSA (see Figure 80.3). Moreover, dyspnea is more frequently reported in OHS patients than in eucapnic OSA patients.

Distinguishing OHS from eucapnic OSA is critical given the greater morbidity and mortality associated with OHS. Compared to patients with OSA, patients with OHS have higher rates of systemic hypertension, congestive heart failure, angina pectoris, and cor pulmonale and are more

likely to be admitted to the ICU and need invasive mechanical ventilation. Therefore, making a timely diagnosis with early initiation of appropriate treatment is important.

DIAGNOSIS

Despite its substantial associated morbidity, the diagnosis of OHS is often overlooked and delayed. The diagnosis of OHS relies on the demonstration of awake hypercapnia with a nocturnal increase in the Pco_2. Chronic hypercapnia may be suggested by an elevated serum bicarbonate level resulting from metabolic compensation, and a serum bicarbonate of 27 mEq/L or greater has been shown to be highly sensitive (92%) but not specific (50%) for hypercapnia. Additionally, significant hypoxemia in OSA patients should raise suspicion for hypercapnia and OHS. Sleep hypoventilation (i.e., > 10 mm Hg increase in $Paco_2$ during sleep above wakefulness) is characteristic of OHS and can be detected in the ICU using serial ABG measurements obtained about every 2 hours during sleep, preferably via an arterial catheter. If an arterial catheter is not used, at a minimum, ABG measurements should be obtained before and after the patient falls asleep.

OHS is a diagnosis of exclusion. It is important to understand the physiologic determinants of alveolar ventilation and $Paco_2$ to rule out other causes of chronic alveolar hypoventilation, including severe obstructive or restrictive pulmonary disease, chest wall disorders like kyphoscoliosis, neuromuscular disease, severe hypothyroidism, and central hypoventilation syndromes (Chapter 1).

Distinguishing chronic obstructive pulmonary disease (COPD) from OHS (as both may present with hypercapnia) is particularly important because the treatment for these conditions differs. Clinical findings common to both include symptoms of dyspnea and fatigue, hypoxemia, chronic respiratory acidosis, polycythemia, and cor pulmonale. Although OHS and COPD may coexist, an absence of significant tobacco history, chest radiograph evidence of hyperinflation, and obstructive spirometry all argue against the presence of significant COPD. Furthermore, approximately 90% of OHS patients exhibit significant sleep apnea and its associated features.

OHS is frequently misdiagnosed as chronic obstructive pulmonary disease (COPD) (Chapter 76). The coexistence of OSA and COPD is referred to as the overlap syndrome and is associated with greater nocturnal hypoxemia, daytime hypercapnia, and risk of pulmonary hypertension than either COPD or OSA alone. In contrast to hypercapnic COPD patients, OHS patients are able to voluntarily hyperventilate and normalize $Paco_2$ below 40 mm Hg. Distinguishing COPD from OHS is particularly important because treatment for these conditions differs. Although the absence of significant tobacco use and lack of hyperinflation on chest radiographs makes COPD less likely, pulmonary function testing should be performed.

Pulmonary function testing and chest imaging are necessary to exclude obstructive and restrictive pulmonary disorders that can cause hypercapnia but are often difficult to perform and interpret in the ICU, especially if patients are intubated. COPD is associated with airflow obstruction with a forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio below the lower limit of normal, whereas in obesity alone the FEV1/FVC ratio is preserved. Reductions in maximal expiratory and inspiratory pressures may suggest neuromuscular disease. Other testing should include thyroid function testing to exclude hypothyroidism and a complete blood count to determine secondary erythrocytosis. Electrocardiography and echocardiography are useful in the assessment of pulmonary artery pressure and right ventricular function.

Patients with severe obstruction resulting from COPD may retain CO_2 while awake and asleep. In addition, their hypercapnia may worsen during sleep, especially while in REM sleep. This is due to REM-induced weakness of the nondiaphragmatic respiratory muscles that they normally use to maintain ventilation. The latter muscles are used because their flattened or inverted diaphragms contribute little to ventilation.

Consider the diagnosis of OHS in all morbidly obese patients; however, remember that not all morbidly obese patients manifest OHS. Morbid obesity adversely impacts respiratory physiology in several ways, including pulmonary mechanics (reduced functional residual capacity, expiratory reserve volume, and total lung capacity), increased upper airway resistance, and increased work of breathing. Importantly, weight gain, in and of itself, does not cause hypercapnia. Patients with OHS have measurable differences in the work of breathing compared to subjects with either obesity or OSA alone. Respiratory muscle strength is reduced in OHS patients and usually normal in obese patients. Compared with a supranormal drive seen in many obese patients, OHS patients have a blunted respiratory drive resulting in hypoventilation. A putative explanatory mechanism is abnormal central ventilatory control associated with resistance to leptin, a hormone that influences both satiety and ventilation. Obese patients have significantly increased levels of leptin compared with the nonobese, which may produce enhanced respiratory drive amid higher ventilatory load. Resistance to these elevated serum leptin levels could trigger the development of diurnal hypercapnia observed in OHS. In addition to alveolar hypoventilation, atelectasis and concomitant V/Q mismatch contribute to the hypoxemia. Another facet of OHS, not typically seen in obesity, is the presence of pulmonary hypertension.

THERAPY

The recognition and subsequent initiation of treatment are critical in OHS patients, who experience increased hospitalizations and mortality compared to obese patients who are normocapnic and to OHS patients treated with non-invasive ventilation. A significant reduction (absolute reduction of 16%) in the rate of reintubation has been in reported in severely obese subjects, especially those with hypercapnia, who are immediately extubated to 48 hours of prophylactic non-invasive (positive pressure) ventilation (NIV) compared to conventional medical therapy. Intubating patients with OHS, as with OSA, can be problematic: approximately 50% of morbidly obese patients requiring emergent intubation for respiratory failure experience a difficult intubation requiring more than three intubation attempts by an experienced clinician. It is recommended that health care providers anticipate these situations by having an experienced clinician/anesthesiologist intubate these patients and consider using a fiberoptic bronchoscope. A laryngeal mask can help to maintain ventilation until a definitive airway has been established.

Treatment of OHS varies depending on the state of the patient at the time of presentation. Patients who present to the ICU in decompensated hypercapnic respiratory failure should be considered for early initiation of NIV (Chapter 3) while treating coexisting medical problems. This may obviate the need for endotracheal intubation and invasive mechanical ventilation, but NIV should not delay emergent tracheal intubation if indicated. NIV success depends on appropriate patient selection and an understanding of the contraindications to NIV (Chapter 3, Table 3.2).

NIV can be applied with conventional critical care ventilators designed for use on intubated ICU patients or portable ventilators designed specifically for home non-invasive ventilation. Both volume- and pressure-cycled ventilators are available. In the morbidly obese patient where higher airway pressures are often necessary to overcome increased respiratory impedance, volume-cycled ventilation may be more appropriate than pressure-cycled ventilation.

Regardless of the mode of ventilation, patients in acute respiratory failure initiated on NIV require close monitoring by appropriately skilled ICU staff. If successful, patients should show improvements in mental status, respiratory distress, pH, $Paco_2$, and hypoxemia within 1 to 3 hours of initiation. Failure to improve or tolerate NIV should prompt consideration for invasive mechanical ventilation. As is the case for correcting elevated $Paco_2$ in hypercapnic patients with acute flares of COPD, one should monitor changes in $Paco_2$ closely to avoid too rapid a correction with resulting alkalemia caused by a posthypercapnic metabolic alkalosis (see Figure B2 in Appendix B).

Successful NIVP treatment depends largely on a good interface. In acute respiratory failure, oronasal masks are generally preferred to minimize leak with the high pressures and tidal volumes often necessary to achieve the increased minute ventilation during sleep. Moreover, patients tend to mouth-breathe in acute respiratory failure. There is, however, a growing variety of available mask interfaces that should be tailored to patient comfort.

No standard protocol for BIPAP titration exists, but it is reasonable to start by increasing the expiratory PAP (EPAP) to eliminate flow limitation and then adding inspiratory PAP (IPAP) to the final EPAP to improve alveolar ventilation. A pressure difference between IPAP and EPAP of at least 8 cm H_2O may be required. In up to half of OHS patients, supplemental oxygen is needed in addition to PAP therapy to maintain oxygen saturation greater than 90% in the absence of airflow limitation. The need for supplemental oxygen may decrease with time. Giving supplemental oxygen alone is not recommended as it may prolong apneas and worsen respiratory acidosis in patients with OHS.

Typically, a nasal or full-face mask (oronasal) interface may be utilized, although options in the ICU may be limited. Full-face masks permit higher pressure settings than nasal masks, although they can prove challenging for patients with anxiety or claustrophobia. Vigilance for both air leak and skin breakdown around the mask-patient interface is important.

The primary end point for NIV in patients with OHS is normalizing the nocturnal and daytime Pco_2 and pH. A daytime Pco_2 of 40 to 50 mm Hg is ideal, although values between 50 and 60 mm Hg may be acceptable. Other clinical end points include patient symptoms and signs (e.g., somnolence and snoring) and oxygenation. In general, higher inspiratory positive airway pressure (IPAP) (10 to 30 cm H_2O) and expiratory positive airway pressure (EPAP) (5 to 15 cm H_2O) are required for OHS than for OSA, and the driving pressure (IPAP – EPAP) should exceed 5 to 10 cm of water. Most patients demonstrate significant clinical improvement within a few hours and achieve near-normal pH values within 24 hours.

To initiate NIV in patients with OHS, either a bi-level or conventional (in the non-invasive mode) ventilator should be utilized. Depending on the status of the patient and the machine mode utilized, a backup respiratory rate is likely imperative. Some commercially available devices can deliver inspiratory pressures up to 40 cm H_2O and entrain 100% oxygen. A conventional ventilator set to the non-invasive mode can deliver a pressure-cycled or volume-cycled breaths. One advantage of conventional ventilators is the battery mode that allows for the continuation of NIV while transporting a patient out of the ICU to another location.

With these parameters stabilized, the patient can be transferred from the ICU. Upon discharge, serial arterial blood gases (ABGs) should be performed to permit therapy adjustments. In the adherent patient, NIV can improve the restrictive pulmonary defects and blunted chemosensitivity characteristic of OHS. If these therapeutic strategies are ineffective, consultation with a weight loss specialist or bariatric surgeon is recommended in addition to a discussion about tracheostomy.

Weight loss, although difficult to sustain, improves multiple aspects of OHS including hypercapnia, hypoxemia, and respiratory muscle function. The dramatic rise in bariatric surgeries being performed in the United States should lead to a better understanding of the physiologic changes in sleep that occur with significant weight loss. Supplemental oxygen alone is ineffective in the treatment of OHS. CPAP successfully treats mild or stable OHS by splinting the upper airway, improving lung volume, and reducing the work of breathing. However, NIV should be utilized in the acute or unstable setting, delivered using pressure-limited or volume-limited modes. Well-designed, controlled studies have not compared pressure- versus volume-cycled ventilation in OHS. Although pressure-limited NIV is typically more comfortable, volume-limited NIV stabilizes minute ventilation amid variable patient effort, airway resistance, and chest wall compliance. It is imperative to examine the contraindications to NIV (including the inability to protect the upper airway, massive gastrointestinal bleeding, hypotension, and facial

trauma) on a case-by-case basis. Close periodic evaluation of the response to NIV is necessary in the first few hours of therapy, including surveillance of vital signs, ABGs, and patient tolerance. Patient-ventilator asynchrony and periodic breathing commonly occur in OHS patients on NIV and may affect treatment efficacy and sleep quality.

Although significant weight reduction improves symptoms and signs of both OSA and OHS and should be encouraged in all obese patients, it is often difficult to achieve and maintain. Bariatric surgery should be strongly considered in the OHS population (Chapter 93). Tracheostomy can improve nocturnal obstructive events and hypercapnia, but the procedure is associated with risks, especially in the obese patient with excess fat around the neck. Tracheostomy is generally reserved for those patients for whom other treatment options have failed, especially those whose daytime hypoventilation persists. Pharmacologic interventions with respiratory stimulants such as medroxyprogesterone or acetazolamide have had minimal success in limited clinical trials. Frequent side effects and a lack of demonstrated long-term benefits of these medications limit their usefulness.

An annotated bibliography can be found at www.expertconsult.com.

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This double-blind, randomized, controlled, crossover trial investigated the effects of 100% oxygen compared with room air in 24 patients with newly diagnosed obesity-associated hypoventilation. The study demonstrated worsening hypercapnia, decreased minute ventilation, and increased volume of dead space to tidal volume ratio with oxygen administration compared with room air, suggesting caution in the administration of supplemental oxygen therapy alone in patients with OHS.

CHAPTER 81

Acute Kidney Injury and Rhabdomyolysis

Rhonda S. King ■ Michael R. Rudnick

Acute kidney injury (AKI) is an abrupt decline in renal function manifested by increased plasma creatinine and increased blood urea nitrogen (BUN) concentrations and a declining urine output. In 2004, the Acute Dialysis Quality Initiative defined AKI using the acronym RIFLE (Figure 81.1) to represent worsening renal function classes. Each letter in RIFLE represents, respectively, *r*isk, *i*njury, *f*ailure, and *l*oss of renal function, and ultimately "E" stands for *e*nd-stage renal disease (ESRD). The RIFLE criteria deem a small increase in the serum creatinine concentration of more than 0.3 mg/dL over one to several days as clinically significant. The frequency of AKI ranges from 2% to 5% in hospitalized general medical-surgical patients to 10% to 25% in patients in the intensive care unit (ICU). The RIFLE criteria are a sensitive definition of acute renal failure, allowing physicians to recognize the increased morbidity and mortality associated with even slight serum creatinine elevations. Although AKI frequently develops as a direct complication of the patient's underlying disease process, the majority of episodes are related to medical care.

AKI increases morbidity and both the length and cost of hospitalization. Patients with AKI have a high mortality rate: 25% in nonoliguric and about 50% in oliguric patients. Death in patients with AKI is attributable not to AKI itself but rather to infections and cardiovascular or respiratory complications. Mortality increases when AKI occurs with sepsis, respiratory failure, and hypotension requiring inotropic support (but not age per se). AKI can lead to chronic kidney disease (CKD) and progression to ESRD and doubles the risk of future cardiovascular events.

Differential Diagnosis

AKI can be divided into three broad pathophysiologic categories: decreased renal perfusion (prerenal AKI), obstruction to urine flow (postrenal AKI), or a renal parenchymal insult (intrinsic AKI). This last category further divides into (1) primary renal diseases involving the vasculature, glomeruli, and tubulointerstitium and (2) acute tubular necrosis.

PRERENAL ACUTE KIDNEY INJURY (AKI)

Any decrease in renal perfusion activates physiologic processes designed to preserve glomerular filtration rate (GFR) and solute excretion. Moderate decreases in perfusion stimulate both neural and hormonal factors (primarily angiotensin II, prostaglandins, catecholamines, aldosterone, and vasopressin), producing selective postglomerular (efferent) arteriolar vasoconstriction. This efferent vasoconstriction maintains GFR and enhances renal sodium reabsorption. However, with more severe and prolonged renal hypoperfusion, these regulatory processes fail to maintain normal GFR, culminating in prerenal AKI (Table 81.1A) and nitrogenous waste accumulation in the blood.

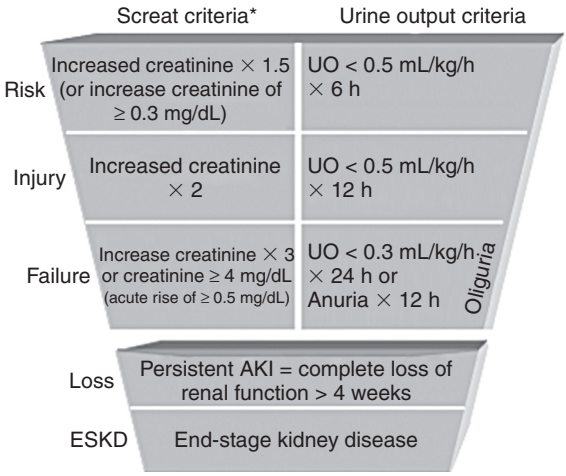


Figure 81.1 The RIFLE criteria for AKI. Screat, serum creatinine concentration; UO, urine output. *(Used with permission from Kellum JA, Bellomo R, Ronco C: Definition and classification of acute kidney injury. Nephron Clin Pract 109:182-187, 2008.)*

TABLE 81.1A ■ **Causes of Prerenal Acute Kidney Injury**

Volume Depletion	Renal Vasoconstriction
Decreased effective arterial blood volume	Cyclosporine
Congestive heart failure	Hepatorenal syndrome
Cirrhosis	Hypercalcemia
Nephrotic syndrome	Nonsteroidal anti-inflammatory drugs (NSAIDs)
	Tacrolimus

True intravascular volume depletion or states depleting effective arteriolar volume (for example, congestive heart failure, cirrhosis, or nephrotic syndrome) can lead to prerenal AKI. In these latter states, diuretic therapy may further compromise renal perfusion by superimposing true volume depletion. Drugs that block homeostatic responses and the aforementioned autoregulatory mechanisms to renal hypoperfusion (angiotensin-converting enzyme inhibitors [ACEIs], angiotensin-receptor blockers [ARBs], and nonsteroidal anti-inflammatory drugs [NSAIDs]) may worsen renal function. Vasoconstrictors (such as catecholamines, cyclosporine, or tacrolimus) potentially decrease renal perfusion and exacerbate prerenal AKI. The hepatorenal syndrome (defined in Table 81.2) results from severe renal vasoconstriction associated with end-stage liver disease (see Chapter 27) and does not improve with volume loading. In the critically ill patient, multiple factors usually contribute to prerenal AKI.

The hallmarks of prerenal AKI are the excretion of a concentrated urine (urine osmolality > 700 mOsm/kg, urine specific gravity > 1.020), with relatively low sodium concentrations (urine sodium < 20 mEq/L [< 20 mmol/L]), fractional excretion of sodium (FENA) less than 1% (see Chapter 39), and rapid reversibility with correction of the underlying cause. FENA should be used cautiously as a strict diagnostic criterion (Table 81.1B), as patients with CKD may be unable to concentrate their urine or achieve a FENA less than 1%. Furthermore, it is extremely important to only use FENA in the setting of *oliguria* (e.g., < 500 mL urine output in 24 hours). Diuretics can also produce a FENA > 1% in patients with prerenal AKI.

Conversely, conditions not defined as prerenal AKI (such as contrast nephropathy, rhabdomyolysis, hemoglobinuria, and urinary tract obstruction) may also have a low FENA (see Table 81.1B).

TABLE 81.1B ■ **False Negatives and False Positives When Using Fractional Excretion of Sodium (FENA) < 1% as a Diagnostic Test for Prerenal Acute Kidney Injury (AKI)**

"False Negatives" (i.e., FENA > 1%* despite *prerenal AKI)
Chronic renal disease with loss of normal concentrating capacity (urine output > 500 mL/day)
Nonoliguric disorders
—Chronic renal disease with loss of sodium reabsorption
—Osmotic diuresis (e.g., resulting from mannitol, glucose)
—Recent diuretic use (e.g., furosemide)
"False Positives" (i.e., FENA < 1%* without *prerenal AKI)
—Contrast nephropathy
—Hemoglobinuria
—Rhabdomyolysis with myoglobinuria
—Urinary tract obstruction (partial)

TABLE 81.2 ■ **Diagnostic Hepatorenal Syndrome Criteria in Cirrhosis**

Cirrhosis with ascites
Serum creatinine > 1.5 mg/dL
No improvement of serum creatinine (decrease to a level of ≤ 1.5 after at least 2 days with diuretic withdrawal and volume expansion with albumin; the recommended dose of albumin is 1 g/kg of body weight per day up to maximum of 100 g/day
Absence of shock
No current or recent treatment with nephrotoxic drugs
Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/day, microhematuria > 50 RBCs per hpf or abnormal renal ultrasound

RBCs, red blood cells; hpf, high-powered field.
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Although prerenal AKI is typically oliguric, in patients with underlying renal insufficiency or renal concentrating defects, urine volumes may exceed 500 mL/day. In addition, diuretic therapy or a solute diuresis from hyperglycemia or protein loading may increase renal sodium excretion, impair renal concentration, and result in nonoliguric AKI.

POSTRENAL ACUTE KIDNEY INJURY (AKI)

Obstruction to urine flow at any level of the urinary collecting system may produce AKI (Table 81.3). Lower urinary tract obstruction may occur at the level of the bladder, bladder outlet, or urethra. Upper urinary tract obstruction may occur at the level of the ureter or the renal pelvis. Upper tract obstruction must be bilateral to cause AKI, absent a single functioning kidney or baseline renal insufficiency. Complete obstruction produces anuria, whereas partial obstruction yields variable urine output, with polyuria or fluctuation between polyuria and anuria characteristic.

Exclude postrenal causes in all patients with AKI, as obstructive renal failure is potentially reversible if promptly diagnosed and decompressed. Demonstrating residual bladder volume after voiding (postvoiding residual) > 100 mL by bladder catheterization is diagnostic of bladder

TABLE 81.3 ■ **Causes of Postrenal Acute Kidney Injury**

Lower Tract Obstruction
Benign prostatic hypertrophy
Bladder cancer
Bladder stones
Blood clot
Neurogenic bladder
Prostate cancer
Urethral stricture
Upper Tract Obstruction (must be bilateral unless there is only one functioning kidney)
Aortic aneurysm
Blood clot
Kidney stone
Pelvic malignancy
Renal papillary necrosis
Retroperitoneal fibrosis
Retroperitoneal tumor
Transitional cell carcinoma

outflow obstruction or a neurogenic bladder. Perform renal ultrasonography to rule out upper tract obstruction evidenced by hydronephrosis.

INTRINSIC ACUTE KIDNEY INJURY (AKI)

Intrinsic renal parenchymal injury producing AKI may be characterized into five broad categories on the basis of the underlying pathogenesis: (1) acute tubular necrosis (ATN), (2) acute interstitial nephritis (AIN), (3) acute glomerulonephritis (AGN), (4) intratubular obstruction, and (5) acute vascular syndromes (Table 81.4). Of these categories, ATN is by far the most common cause of intrinsic AKI.

Acute Tubular Necrosis (ATN)

ATN is characterized pathologically by injury and death of renal tubular epithelial cells. Intratubular obstruction by exfoliated necrotic cells, back leakage of glomerular filtrate through the damaged tubular epithelium, and a decreased GFR from reactive vasoconstriction all contribute to renal excretory failure.

ATN divides equally between ischemic and nephrotoxic injuries. Substantial variability exists in the renal response to ischemia: in some patients, a few minutes of ischemia may produce ATN, whereas in others, prolonged renal hypoperfusion produces only transient prerenal azotemia. Although any cause of prerenal AKI may progress to ischemic ATN, most cases are associated with a period of frank hypotension. Risk factors for ischemic ATN include sepsis, major surgery (especially cardiopulmonary bypass, abdominal aortic aneurysm repair, and biliary procedures), preexisting CKD, and treatment with ACEIs, ARBs, and NSAIDs.

Agents that can produce nephrotoxic ATN include aminoglycoside antibiotics, amphotericin B, acetaminophen, cisplatin, radiocontrast media, possibly free hemoglobin, and myoglobin. Contrast-induced nephropathy is the most common to cause ATN. In most ICU patients, ATN is multifactorial, resulting from a combination of nephrotoxic and ischemic insults.

TABLE 81.4 ■ **Causes of Intrinsic Acute Kidney Injury**

Acute Tubular Necrosis
Ischemic
Cardiopulmonary arrest
Hypotension
Hypovolemic shock
Sepsis
Nephrotoxic
Drug-induced (acetaminophen, aminoglycosides, amphotericin B, cisplatin, IV radiocontrast agents)
Pigment nephropathy (hemoglobin, myoglobin)
Acute Interstitial Nephritis
Drug Induced
Cephalosporins
Cimetidine
Ciprofloxacin
Furosemide
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Penicillins
Phenytoin
Proton pump inhibitors
Sulfonamides
Infection Related
Bacterial infection
Mycobacterial infection
Rickettsial infection
Viral infection
Acute Glomerulonephritis
Endocarditis-associated glomerulonephritis
Hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) (Chapter 63)
Postinfectious glomerulonephritis
Rapidly progressive (crescentic) glomerulonephritis (e.g., Goodpasture syndrome, poststreptococcal glomerulonephritis)
Systemic vasculitis (acute lupus nephritis, polyarteritis nodosa, Henoch-Schönlein purpura, Wegener's granulomatosis, cryoglobulinemia)
Intratubular Obstruction
Ethylene glycol ingestion (producing oxalate crystals)
Multiple myeloma
Tumor lysis syndrome
Crystals from acyclovir
Acute Vascular Syndromes
Cholesterol emboli
Malignant hypertension
Renal artery thromboembolism
Renal vein thrombosis
Scleroderma renal crisis

Patients with preexisting CKD and older patients are at increased risk for the development of ATN and are less likely to recover renal function after ATN. Similarly, volume depleting and vasoconstricting agents each increase the risk of ATN from other causes.

Depending on the severity of parenchymal injury, ATN may be either oliguric or nonoliguric. The loss of tubular integrity destroys both urinary concentrating and diluting ability. Thus, urine osmolality is approximately 300 mOsm/kg (isosthenuria) and urine-specific gravity is approximately 1.010. Similarly, impaired tubular sodium reabsorption results in a urine sodium concentration that generally exceeds 40 mEq/L (40 mmol/L) and a FENA greater than 1%. The presence of muddy brown casts and renal tubular epithelial cells, both alone and in casts, differentiates ATN from prerenal AKI.

Acute Interstitial Nephritis (AIN)

AIN is characterized by inflammation of the renal interstitium and tubules, with a lymphocytic and eosinophilic infiltrate typically seen on biopsy. The clinical triad of fever, rash, and eosinophilia is classically associated with AIN, but one or more components are frequently absent. Most cases of AIN result from drug hypersensitivity to penicillins, cephalosporin and sulfa antibiotics, diuretics, anticonvulsants, NSAIDs, proton pump inhibitors, and histamine receptor type 2 blockers, although almost any medication can be implicated. Less commonly, AIN develops as an immune reaction to an infection. Patients with AIN are usually nonoliguric, with a slower increase in serum creatinine concentrations than patients with ATN. The AIN urine sediment usually demonstrates sterile pyuria, hematuria, and white blood cell casts. Eosinophiluria may be present and is best demonstrated using a stain specific for eosinophils (Hansel stain).

AIN associated with NSAIDs commonly presents without an associated fever, rash, or eosinophilia. In addition, nephrotic-range proteinuria may be present in AIN associated with NSAIDs but not from other causes.

Acute Glomerulonephritis (AGN)

A variety of glomerular syndromes may present with acute (progressing over hours to days) or subacute (progressing over days to weeks) renal failure (see Table 81.4). Goodpasture syndrome is the specific association of antiglomerular basement membrane antibody (anti-GBM) and rapidly progressive (crescentic) glomerulonephritis with pulmonary hemorrhage. The characteristic feature of the glomerulonephritides is the presence of a nephritic urine sediment characterized by dysmorphic red blood cells and in some cases red blood cell casts, along with some degree of proteinuria. Measurement of serum complement and serologic studies (e.g., antinuclear antibody [ANA]), antineutrophil cytoplasmic antibody [ANCA], cryoglobulins, and anti-GBM) may suggest a diagnosis. Complement levels represent a good first test to help narrow the differential diagnosis, since decreased levels suggest immune complex–mediated glomerulonephritides including lupus, postinfectious, endocarditis, hepatitis C–related mixed cryoglobulinemic glomerulonephritis, and membranoproliferative glomerulonephritis (MPGN). However, renal biopsy is usually necessary to definitively diagnose the type of glomerulonephritis.

Intratubular Obstruction

Intratubular obstruction by crystal deposition or paraproteins may produce AKI. Acute uric acid nephropathy most commonly occurs in tumor lysis syndrome after chemotherapy of sensitive tumors. The *tumor lysis syndrome* is usually associated with hyperkalemia, hyperphosphatemia, and severe hyperuricemia (serum uric acid concentrations > 20 mg/dL [1200 μmol/L]), and microscopic examination of the urine demonstrates many uric acid crystals. Ethylene glycol ingestion (see Chapter 57) may produce acute oxalate nephropathy, characterized by heavy oxalate crystalluria. Intratubular precipitation of methotrexate, indinavir, and acyclovir may also produce AKI.

Patients with multiple myeloma risk AKI from a number of causes, including hypercalcemia, hyperuricemia, and direct nephrotoxicity from immunoglobulin light chains. Classically, acute

myeloma of the kidney produces widespread intratubular precipitation of light chains and tubular atrophy and is diagnosed by demonstrating a serum paraprotein or light chain in the urine.

ACUTE VASCULAR SYNDROMES

Partial or complete renovascular occlusion from renal artery thromboembolism or thrombosis, arteriolar spasm in malignant hypertension, scleroderma renal crisis, or cholesterol emboli may cause AKI. Atheroembolic renal failure is frequently associated with fever, livedo reticularis, lower extremity petechiae, eosinophilia, and hypocomplementemia. Patients who develop atheroembolic disease often complain of decreased appetite and weight loss and have evidence of bowel ischemia as well. Atheroembolic AKI occurs most commonly after angiography and aortic surgery, although atheroemboli may develop spontaneously. Rarely acute renal vein thrombosis can cause AKI.

DIFFERENTIAL DIAGNOSIS OF AKI

The clinical history and physical examination guide the differential diagnosis of intrinsic AKI. Pay careful attention to medications administered preceding the onset of AKI, episodes of sepsis or hypotension, and the administration of nephrotoxins. Examination of the urine sediment and urine electrolytes in the setting of oliguria narrows the differential diagnosis. A positive dipstick test for blood in the absence of red blood cells on microscopy suggests rhabdomyolysis (with myoglobinuria causing the false-positive dip stick result for blood) or intravascular hemolysis. As noted previously, red blood cell casts or dysmorphic red blood cells indicate glomerulonephritis. In AIN, the urine usually contains red and white cells, and white cell casts. Although bacteria may not be seen, a urine culture should be performed to exclude pyelonephritis or lower urinary tract infection. The presence of eosinophiluria suggests interstitial nephritis, but also can be present with atheroembolic disease. Heavy crystalluria may also guide the diagnosis: bipyramidal (envelope-shaped) calcium oxalate crystals suggest ethylene glycol poisoning; rhomboidal (polarizable) uric acid crystals suggest tumor lysis syndrome. A positive sulfosalicylic acid test result for protein in the setting of a negative dipstick test result for protein suggests myeloma kidney. Consider obstruction in every patient with AKI, and if the course of AKI does not coincide with the clinical picture, obtain a renal ultrasound to rule out hydronephrosis. Renal biopsy is rarely necessary in the diagnosis of AKI. Limit biopsies to patients in whom a diagnosis of glomerulonephritis or AIN is considered and to patients with persistent, unexplained AKI.

Management

PRERENAL ACUTE KIDNEY INJURY (AKI)

The treatment of prerenal AKI is the restoration of normal renal perfusion. Hypovolemic patients should receive fluid resuscitation with blood products, colloid, or isotonic crystalloid as appropriate. Poor cardiac function producing AKI may require inotropic support and afterload reduction. In patients with severe cirrhosis, effective volume depletion may occur despite total body volume overload. Carefully monitor volume replacement in cirrhotic patients. Multiple studies demonstrate octreotide and midodrine effective (with or without albumin) in treating hepatorenal syndrome. Octreotide and midodrine improve renal function, reduce mortality, and bridge patients to liver transplantation; titrate the dose of midodrine to achieve a goal blood pressure. The clinical presentation may not differentiate between simple prerenal azotemia and the hepatorenal syndrome. In this setting, central venous or pulmonary artery pressure monitoring may help guide fluid therapy and prevent iatrogenic pulmonary edema. In all patients with prerenal azotemia, discontinue diuretics and NSAIDs and avoid ACEIs, aldosterone antagonists, and ARBs.

POSTRENAL ACUTE KIDNEY INJURY (AKI)

Postrenal AKI treatment consists of relieving the obstruction. Bladder catheterization relieves obstruction in patients with bladder outlet obstruction or neurogenic bladder. Upper tract obstruction requires ureteral stents or percutaneous nephrostomies.

After relief of the obstruction, a postobstructive diuresis may occur. To the extent that water and sodium build up during the course of the AKI, the polyuria is physiologic and corrects this overload. In some patients, an osmotic postobstructive diuresis occurs from retained urea and volume replacement may be necessary. Rarely, however, residual tubular injury results in urinary concentrating defects, renal salt wasting, or both and can lead to volume contraction and hypernatremia. Therefore, closely monitor urine output, volume status, and serum electrolytes after relief of obstruction. In volume overload, only partially replace urine output to permit negative fluid balance. In euvolemic patients, completely replace urine output but ensure that excessive fluid administration does not drive the polyuria. The urine electrolyte composition should guide the composition of the replacement fluid. Absent such measurements, 0.45% saline (i.e., half normal) is an appropriate initial replacement solution. After relief of obstruction, patients may have potassium secretory deficits or renal potassium wasting, leading to hyperkalemia or hypokalemia, respectively. These patients may also acquire a renal tubular acidosis or renal phosphate wasting. Therefore, potassium, bicarbonate, and phosphate replacement must be guided by serum and urine electrolyte measurements.

INTRINSIC ACUTE KIDNEY INJURY (AKI)

Supportive Measures

Supportive measures are the mainstay of therapy for all forms of intrinsic AKI. Administer fluids to correct hypovolemia and then replace obligate losses. Diuretic administration facilitates the treatment of volume overload in nonoliguric AKI. However, randomized controlled trials demonstrate that the use of furosemide in AKI does not reduce in-hospital mortality, the risk for requiring continuous renal replacement therapy, or the number of dialysis sessions. Although some studies suggest that furosemide can change oliguric to nonoliguric AKI, it remains unclear whether this response was related to a less severe form of AKI with improvement in ATN. Avoid high-dose furosemide (range 1 to 3.4 g daily) that risks temporary deafness and tinnitus. A maximum dose of 160 mg furosemide intravenously is recommended, as higher doses do not produce any additional natriuresis in patients with extremely low GFR. Monitor serum electrolytes closely, and replace bicarbonate to treat metabolic acidosis. Discontinue routine potassium supplements, and treat hyperkalemia (see Chapter 39). Restrict phosphate intake, and give oral binders (e.g., calcium carbonate, calcium acetate, lanthanum, or aluminum hydroxide) to reduce elevated phosphate levels. Avoid Bicitra (citric acid/sodium citrate) and aluminum hydroxide administration together, as citrate increases aluminum absorption.

Discontinue or avoid nephrotoxins such as aminoglycosides, antibiotics, and intravenous (IV) radiocontrast media, if possible. Also avoid medications that reduce renal perfusion, such as ACEIs, ARBs, and NSAIDs. Adjust all medication dosages for renal failure, and monitor blood levels when possible (see Chapter 17). Remember with the sudden onset of oliguria/anuria, several days are required for the serum creatinine to rise to stable levels. Thus, in this non-steady-state setting, the initial GFR determination is essentially zero and should not be calculated from the serum creatinine.

AKI is a hypercatabolic state. Protein loading does not, however, result in positive or even neutral nitrogen balance. Rather, it may exacerbate azotemia and accelerate the need for dialysis. The optimal nutritional protein prescription therefore remains controversial, with protein recommendations generally ranging between 1.2 and 1.5 g/kg predicted body weight/day (Chapter 15).

When using parenteral nutrition, pay careful attention to the electrolyte formulations. Most standard electrolyte formulations contain excessive potassium, phosphate, and magnesium for a patient with renal failure.

Many patients require renal replacement therapy during their AKI (see Chapter 20). Indications for initiation of dialysis include diuretic-resistant volume overload, metabolic acidosis or hyperkalemia unresponsive to medical therapy, uremic symptoms (e.g., mental status changes, pericarditis), otherwise unresponsive uremic-exacerbated bleeding (Chapter 26), and severe azotemic symptoms. Although no level of BUN and creatinine serves as an absolute requirement for the initiation of dialysis, a BUN > 100 mg/dL or a creatinine level > 6 to 7 mg/dL is generally accepted as an indication for dialysis. Neither earlier initiation of dialysis nor more "intensive" dialysis (versus traditional time of starting and intensity of dialysis) improves survival or recovery from AKI.

Acute Tubular Necrosis (ATN)

No nonsupportive therapy has been proven effective for ATN, and management remains primarily supportive care. Although oliguric ATN carries a higher mortality rate than nonoliguric ATN, the controversy persists whether diuretic-induced diuresis in an oliguric patient improves outcome or merely identifies patients with less severe tubular injury. Conversion to a nonoliguric state does, however, simplify fluid management and may delay the need for dialysis. Because loop diuretics (e.g., furosemide, bumetanide) act from the luminal side of the tubule, high doses (e.g., up to 160 mg of IV furosemide as a bolus or 20 to 40 mg/hour as a continuous infusion) may be required to achieve diuresis in patients with reduced GFR. The newer loop-acting diuretics are no more efficacious than furosemide at equipotent doses, but all are substantially more expensive. Combining a loop-acting diuretic with oral metolazone or an IV thiazide diuretic (e.g., chlorothiazide) may be synergistic.

In many circumstances, the best treatment for ATN is prevention. Avoid nephrotoxic agents whenever possible. Monitor aminoglycoside dosing closely to prevent toxic drug levels (see Chapter 17). Many agents, including aminoglycosides, amphotericin B, and IV radiocontrast media, commonly cause ATN in the setting of volume depletion; saline loading may therefore decrease the risk of ATN. To prevent contrast-induced nephropathy (CIN), administer isotonic saline before and after contrast media injections. Both isotonic sodium bicarbonate and N-acetylcysteine (NAC) have been suggested to reduce CIN, but definitive efficacy studies are lacking.

Acute Interstitial Nephritis (AIN)

The treatment of AIN consists of the discontinuation of any offending medication, including changing to another antimicrobial therapy for any underlying infection if an anti-infective agent appears implicated. If treated before the development of interstitial fibrosis, the renal failure is usually reversible. No randomized controlled trials confirm the hypothesis that steroid therapy hastens and leads to a more complete renal recovery. Thus, steroid therapy is recommended in patients with AIN who fail to improve with discontinuation of the offending drug or who present with severe renal failure.

ACUTE GLOMERULONEPHRITIS

The treatment of acute glomerulonephritis depends on the underlying cause and should be guided by renal biopsy results. The self-limited AKI associated with poststreptococcal, postinfectious, and endocarditis-associated glomerulonephritis usually requires no specific therapy other than treatment of the underlying infection. Acute glomerulonephritis associated with lupus or systemic vasculitis and rapidly progressive (crescentic) glomerulonephritis are usually treated with steroids and cytotoxic agents. Plasmapheresis benefits patients with anti-GBM disease, hemolytic uremic

syndrome, pauci-immune glomerulonephritides, and thrombotic thrombocytopenic purpura (TTP) (see Chapter 63).

INTRATUBULAR OBSTRUCTION

Treat ethylene glycol poisoning with IV sodium bicarbonate to correct the metabolic acidosis, ethanol or 4-methylpyrazole to inhibit metabolism, and emergent hemodialysis (see Chapter 57 for more details). Although much more expensive, 4-methylpyrazole infusion is preferred over ethanol. Prompt initiation of therapy may prevent or attenuate AKI.

In the tumor lysis syndromes, pretreatment with allopurinol and forced saline diuresis may prevent AKI. Bicarbonate containing fluids can be used as well but risk precipitation of calcium and phosphate. Intensive hemodialysis to lower serum uric acid levels should be initiated in patients when acute urate nephropathy develops.

Treat AKI in multiple myeloma with aggressive hydration (2 to 3 liters of normal saline per day) and initiation of chemotherapy to reduce light-chain production. Alkalinization of the urine remains controversial because it may risk precipitating calcium and phosphate. Avoid diuretics because of the potential for increasing intraluminal obstruction from Bence Jones proteins, and treat the associated hypercalcemia and hyperuricemia. Whether acutely lowering circulating paraproteins by plasmapheresis can reverse AKI remains uncertain.

Acute Vascular Syndromes

No effective therapy exists for atheroembolic (cholesterol emboli) AKI. Anticoagulation confers no benefit and may exacerbate the condition. Thrombolytic therapy of acute renal artery thrombosis and thromboembolism may permit revascularization but is frequently associated with persistent renal dysfunction. Treat AKI associated with malignant hypertension with prompt antihypertensive therapy. Scleroderma renal crisis should be treated with ACE inhibitors.

Rhabdomyolysis

Rhabdomyolysis is the clinical syndrome that results from skeletal muscle injury and the release of muscle cell contents. Most cases are subclinical, with the diagnosis generally based on elevations in the serum concentrations of released cellular contents, particularly creatine phosphokinase (CPK), lactic dehydrogenase (LDH), or serum aspartate aminotransferase (AST). In severe cases, overt myoglobinuria (manifested as red or brown urine testing positive for blood on dipstick but without red blood cells on microscopic examination) may be seen. ATN, the most serious potential complication of rhabdomyolysis, develops in only a minority of patients as the result of multiple postulated factors, including intratubular obstruction from myoglobin casts, arteriolar vasoconstriction, and direct tubular cell toxicity.

ETIOLOGY AND CLINICAL AND LABORATORY FEATURES

The causes of rhabdomyolysis can be broadly divided into traumatic and nontraumatic categories (Table 81.5). Although classically associated with severe trauma and crush injuries, the majority of cases of rhabdomyolysis are nontraumatic. Presenting symptoms usually reflect the primary disease process with superimposed weakness, myalgia, and muscle tenderness. Physical findings consist of tender, "doughy" feeling muscles, edema, and muscle weakness. In severe cases, compartment syndromes may develop with signs and symptoms of neurovascular compromise. A sustained intracompartmental pressure > 40 mm Hg indicates the need for fasciotomy (see Chapter 98).

Severe hyperkalemia, hyperphosphatemia, and hyperuricemia are commonly seen with AKI developing from rhabdomyolysis (Chapter 39). Profound hypocalcemia results from calcium salt

TABLE 81.5 ■ **Causes of Rhabdomyolysis**

Traumatic	Malignant hyperthermia
Burns	Muscle ischemia
Crush injuries	—Carbon monoxide poisoning
Nontraumatic	—Carnitine palmitoyl transferase deficiency
Electrolyte Disorders	—McArdle disease
—Hyperglycemia	—Vascular occlusion Metabolic disorders
—Hypokalemia	Medications, drugs
—Hypophosphatemia	—Alcohol
Excessive muscular activity	—Cocaine
Heat stroke	—Gemfibrozil
Immobilization, passive compression	—HMG CoA reductase inhibitors (statins)
Infections	Neuroleptic malignant syndrome
—Gangrene, myonecrosis	Seizures
—Viral myositis	Vigorous exercise

deposition in injured muscle and changes in vitamin D and parathyroid hormone metabolism induced by severe hyperphosphatemia. However, the hypocalcemia does not require specific therapy unless symptomatic, as during the recovery phase mobilization of previously deposited calcium occurs and can even result in hypercalcemia. In this latter setting, hypercalcemia may itself induce AKI from vasoconstriction.

CPK levels elevated to greater than 5000 IU/L (80 μkat/L) are associated with an increased risk of AKI. Plasma creatinine levels rise more rapidly with rhabdomyolysis than from other causes of AKI, up to 2.5 mg/dL per day, caused by the release of creatine from muscle. Volume depletion and acidemia may contribute to development of renal failure. Although myoglobin was traditionally believed to be the most important tubular toxin in rhabdomyolysis, purified myoglobin is relatively nontoxic in the absence of volume depletion.

THERAPY

The most important therapeutic intervention is aggressive volume expansion, to prevent the development of AKI. There is mixed evidence on urinary alkalinization and forced diuresis with mannitol. Alkalinized urine can inhibit precipitation of myoglobin in the renal tubules. However, metabolic alkalosis may exacerbate hypocalcemia and cause calcium phosphate deposition in the tissues. Mannitol and loop-acting diuretics are of unproven benefit in preventing AKI, and mannitol can lead to hyperosmolarity with volume overload and hyperkalemia. When significant renal failure develops, early dialysis is frequently necessary to control hyperkalemia and other metabolic disturbances.

Clinical Pearls and Pitfalls

1. The FENA differentiates prerenal azotemia from other causes of oliguric AKI. However, diuretics or underlying renal insufficiency can elevate the FENA. A low FENA remains helpful in these populations, but a high FENA would be misleading (i.e., a false negative). In addition, other forms of AKI (from contrast, calcineurin inhibitors, pigments, and obstruction) may be associated with a low FENA (i.e., representing a false positive).

TABLE 81.6 ■ **Causes of Azotemia (Increased Blood Urea Nitrogen)**

Corticosteroid therapy	Protein overfeeding
Gastrointestinal hemorrhage	Renal failure
Hypercatabolic state	Tetracycline antibiotics

2. Not all azotemia is renal failure. The BUN can be elevated absent a significant reduction in GFR (Table 81.6).
3. Patients with renovascular disease, or with accelerated or malignant hypertension, may require a higher blood pressure to maintain renal perfusion. Decreasing blood pressure too rapidly or to normal risks development of prerenal AKI.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 82

Diabetic Ketoacidosis, Hyperglycemic Hyperosmolar State, and Alcoholic Ketoacidosis

Gbemisola A. Adeseun ■ Debbie L. Cohen

Diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar state (HHS), and alcoholic ketoacidosis (AKA) are disease entities that are commonly characterized by severe fluid, electrolyte, and acid-base derangements, often prompting evaluation and management in an intensive care unit (ICU). Understanding the pathophysiology of these conditions is crucial for rapid diagnosis and treatment. This chapter describes the important differences among these three disorders.

Diabetic Ketoacidosis

DEFINITION

Diabetic ketoacidosis is defined by the presence of the following: hyperglycemia (blood glucose > 250 mg/dL), metabolic acidosis (arterial blood pH < 7.3 or bicarbonate < 16 mEq/L), and ketonemia (serum ketones ≥ 1:2 dilution) (Table 82.1). Although most patients with DKA have type 1 diabetes, DKA may also occur in patients with type 2 diabetes. African-American patients with type 2 diabetes appear to be particularly vulnerable, as evidenced by rising rates of DKA in this population. DKA remains a significant source of morbidity, accounting for as many as 9% of hospital admissions among patients with an established diagnosis of diabetes.

The presence of DKA leads to a new diagnosis of diabetes in up to 20% of patients. Fortunately, mortality attributable to DKA is generally less than 5% with appropriate treatment. Notably, geriatric patients are vulnerable to adverse outcomes, particularly when coexisting illnesses such as sepsis and myocardial infarction are also present.

PATHOGENESIS

Diabetic ketoacidosis occurs when insulin deficiency and counter-regulatory hormone excess are present simultaneously. Glucagon is the most important counter-regulatory hormone, but other hormones in this category include cortisol, growth hormone, and epinephrine (Figure 82.1). As a result of this hormonal imbalance, there is increased glucose production via gluconeogenesis and glycogenolysis while glucose utilization in peripheral tissues is impaired. The hormonal milieu also favors the liberation of fatty acids that are subsequently oxidized to form ketones. The ketones, β-hydroxybutyrate and acetoacetate, account for the anion gap metabolic acidosis that is characteristic of DKA (Chapter 83). As glucose and ketones accumulate in the

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TABLE 82.1 ■ **Comparison of Diabetic Ketoacidosis, Hyperglycemic Hyperosmolar State, and Alcoholic Ketoacidosis**

Variable	Diabetic Ketoacidosis	Hyperglycemic Hyperosmolar State	Alcoholic Ketoacidosis
Serum glucose	250–600 mg/dL	> 600 mg/dL	Low or normal (but 10% with glucose > 250 mg/dL)
Serum ketones	+ in 1:2 or greater dilution	Absent or mild	May be absent when testing only for acetoacetate
Acidosis	Present (pH < 7.3 with serum [HCO_3^-] < 16 mEq/L)	Absent or mild	Present (but pH may be normal or elevated)
Type of acidosis	Anion gap alone (or mixed anion gap, hyperchloremic)	Anion gap due to ketoacidosis or lactate acidosis (due to poor perfusion)	Anion gap often with respiratory and metabolic alkaloses (see text for details)
History	90% with diabetes (most often type 1)	50% with diabetes (most often type 2)	Nondiabetic chronic alcohol users who binge and then fast 1–2 days

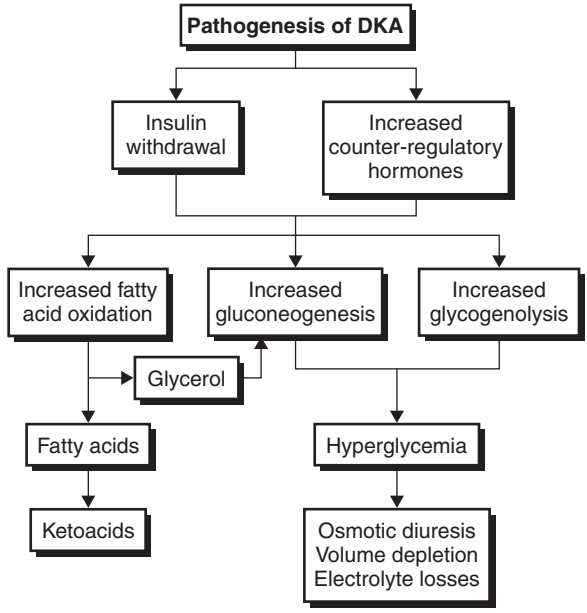


Figure 82.1 Schematic diagram illustrating the pathogenesis of diabetic ketoacidosis.

bloodstream, the reabsorptive threshold of the renal tubule is surpassed, resulting in glucosuria and ketonuria, respectively. The ensuing osmotic diuresis results in the loss of sodium, potassium, and water in the urine. Nonadherence with an insulin regimen frequently causes DKA, but other triggers must be sought. Infections, particularly urinary tract infections (UTIs), and pneumonia, myocardial ischemia, stroke, pancreatitis, drugs, and alcohol consumption commonly precipitate DKA.

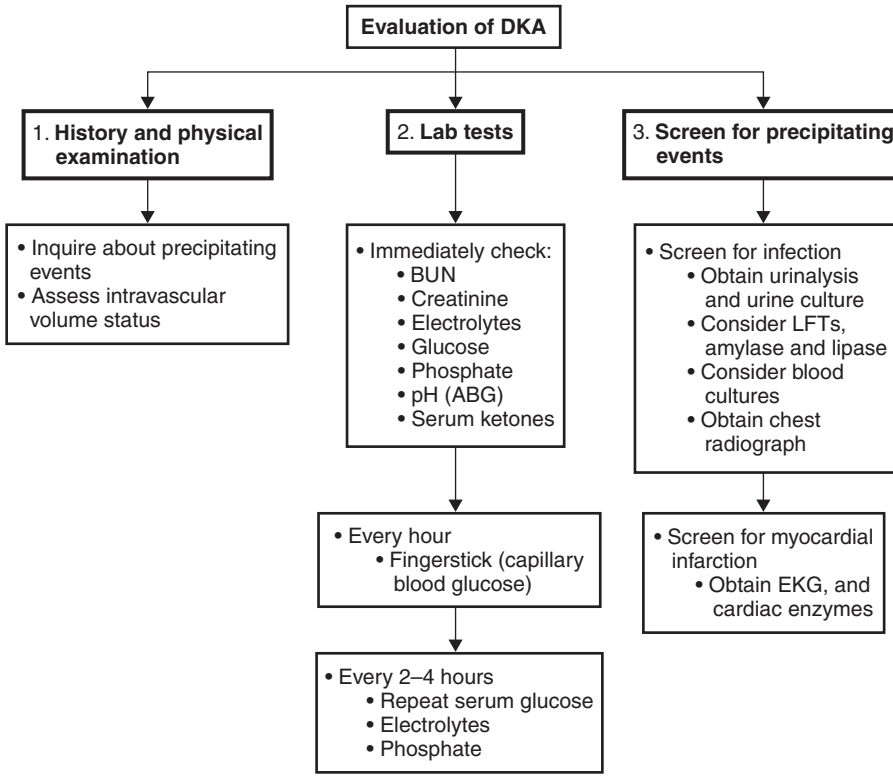


Figure 82.2 Schematic diagram for evaluation of diabetic ketoacidosis. *(Adapted from Kitbachi AE, Umpierrez GE, Murphy MB, et al: Management of hyperglycemic crisis in patients with diabetes. Diabetes Care 24:131-153, 2001).*

EVALUATION

A thorough but rapid history is essential to determine the severity and duration of symptoms as well as to identify any precipitating events or comorbid illnesses. A schematic diagram for evaluation of the patient admitted to the ICU for DKA is shown in Figure 82.2. Presenting symptoms include polyuria and polydipsia that are a consequence of the hyperglycemia-induced osmotic diuresis. Gastrointestinal symptoms such as nausea, vomiting, and abdominal pain are common and are thought to be due to a combination of metabolic acidosis and ileus. Some patients may also report dyspnea due to the acidosis-induced increase in respiratory drive, which produces Kussmaul breathing/respirations.

The physical examination is usually notable for signs of volume depletion—namely, dry mucous membranes, loss of normal skin turgor, tachycardia, and orthostatic hypotension. Deep and rapid respirations (Kussmaul respirations) may be evident. Mild abdominal tenderness is common, but focal abdominal pain or peritoneal signs warrant immediate evaluation. Temperature is normal or mildly hypothermic. Thus, the presence of fever should prompt an evaluation for concurrent infection. Acetone causes a fruity odor that may be detected on the patient's breath. Importantly, acetone can be present in other disorders (e.g., alcoholic or starvation ketoacidosis and isopropyl alcohol ingestion). Altered sensorium is *not* characteristic of DKA and, if present, should trigger further evaluation.

Laboratory analysis demonstrates hyperglycemia. The serum glucose level is usually between 250 and 600 mg/dL (14 to 33 mmol/L). Profound hyperglycemia does not usually occur in DKA because the acidosis causes symptoms that prompt patients to seek medical care relatively early. Hyperglycemia causes an osmotic diuresis resulting in volume depletion, often with a concomitant free water deficit. As renal perfusion and the glomerular filtration rate (GFR) fall, the kidney excretes less glucose, which exacerbates the hyperglycemia.

The acute metabolic acidosis of DKA typically is accompanied by an acute respiratory compensation. Although the acidosis is most commonly an anion gap acidosis, a simultaneous anion gap and nonanion gap acidosis may coexist; or rarely a pure nonanion gap acidosis may be found (see Chapter 83 on metabolic acidoses). The type of acidosis depends on the intravascular volume of the patient. If fluid intake is adequate and GFR preserved, the kidney excretes ketones, thus reducing accumulation of unmeasured anions that would contribute to the serum anion gap. The observed nonanion gap metabolic acidosis is due to ketonuria, which is akin to the loss of bicarbonate equivalents in the urine. On the other hand, patients who are volume depleted have less ketonuria and accumulate more serum ketones, resulting in an anion gap metabolic acidosis. Depending on the volume status, patients with DKA can fall anywhere along this spectrum.

Serum ketones are present in a 1:2 dilution or higher. β-Hydroxybutyrate predominates with a concentration threefold higher than acetoacetate. The assay for ketones relies on the nitroprusside reaction, which only measures acetoacetate. Because acetoacetate only accounts for a small proportion of the ketones that are present, the assay for ketones may be negative early on. The test for ketones may become increasingly positive during the course of treatment, but this reflects a shift from β-hydroxybutyrate to acetoacetate rather than worsening ketonemia. Occasionally, drugs such as captopril can interfere with the assay for ketones, causing a false-positive result.

Patients may have hyperkalemia. This occurs due to insulin deficiency and acidosis, both of which favor a transcellular shift of potassium into the extracellular fluid. Despite the initial elevation in serum potassium level, the majority of patients have total body potassium depletion. The osmotic diuresis causes obligate potassium loss in the urine, and gastrointestinal losses may also contribute to the potassium deficit, averaging 3 to 5 mEq/kg. Initiation of insulin may unmask the potassium deficit as insulin drives potassium intracellularly. An analogous process occurs with phosphate—that is, phosphate levels may be elevated initially, but they typically drop with treatment. Mild leukocytosis is common in DKA, but white blood cell counts greater than 25,000/μL should raise suspicion of an underlying infection.

TREATMENT

The treatment and management of DKA are outlined in Figure 82.3. The following treatment steps are the cornerstones of management: (1) volume resuscitation, (2) reversal of hyperglycemia, (3) inhibition of ketogenesis, and (4) repletion of electrolytes.

VOLUME RESUSCITATION

The average volume deficit is 3 to 4 L. At least 1 to 2 L of isotonic fluid (usually normal saline) should be administered rapidly. Patients with hemodynamic compromise should continue to receive volume resuscitation at a rate of 1 L/hour while their volume status is simultaneously monitored very closely. After adequate repletion of intravascular volume (as judged clinically), patients with a low serum sodium concentration should continue to receive isotonic fluid, but at a slower rate. Fluids are infused at 4 to 14 mL/kg/h, depending on the clinical assessment of volume status. On the other hand, if the serum sodium concentration is normal or elevated, the patient almost certainly has a concomitant free water deficit and the intravenous fluid therapy should be changed to 0.45% saline, also infused at a rate of 4 to 14 mL/kg/h. Serum osmolality should be

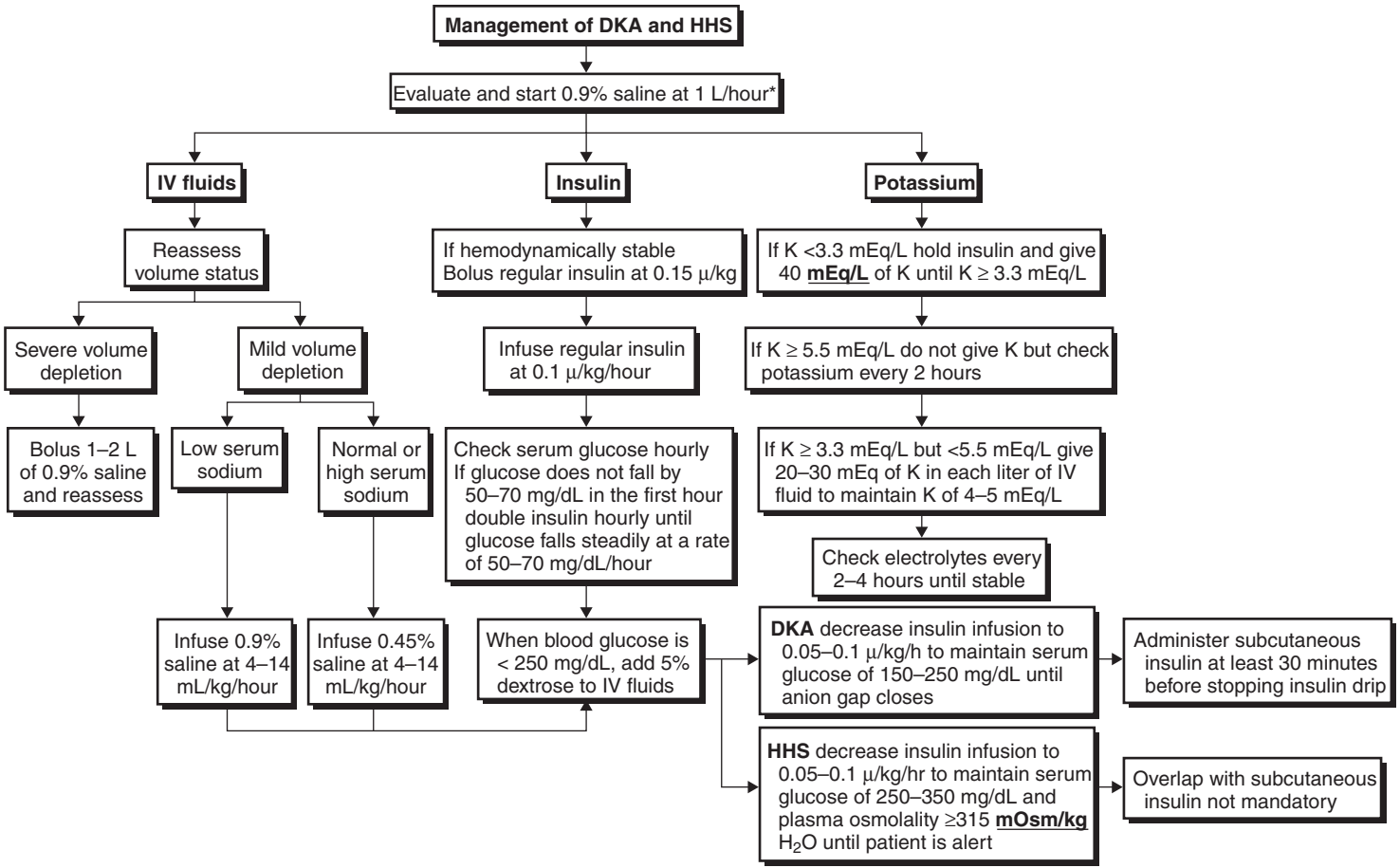


Figure 82.3 Schematic diagram for management of diabetic ketoacidosis and hyperglycemic hyperosmolar state.

corrected no faster than 3 mOsm per hour to avoid iatrogenic cerebral edema. The importance of frequent reassessments of volume status cannot be overemphasized, particularly for patients with a history of heart or renal failure.

REVERSAL OF HYPERGLYCEMIA

Insulin therapy should begin only after initial volume replacement. Hyperglycemia serves to "drag" water into the extracellular fluid (ECF) space (due to its contribution to osmotic pressure in the ECF) and helps maintain blood pressure, even in the face of significant volume deficits. If the volume deficit is not addressed first, insulin administration can precipitate vascular collapse as hyperglycemia resolves and extravascular water moves intracellularly. This occurs more commonly in patients with hyperglycemic hyperosmolar state (HHS) due to the profound hyperglycemia, but it can also occur in patients with DKA. Further, volume resuscitation alone may improve GFR and glucose excretion. Because there is no convincing evidence that withholding insulin for the first 15 to 30 minutes of volume resuscitation has any adverse effects, insulin administration should be delayed during this critical period.

After initial volume repletion, a bolus of 0.15 units/kg of insulin should be given intravenously and a maintenance infusion begun at 0.1 units/kg/h. Capillary blood glucose should be monitored hourly and verified by frequent measurements of serum glucose. If blood glucose does not fall by 50 to 70 mg/dL/h, the insulin drip should be adjusted accordingly. Most ICUs have a protocol for insulin drip titration.

INHIBITION OF KETOGENESIS

Insulin is required to inhibit lipolysis and ketone generation. Because the serum glucose normalizes before ketoacid production stops, it is important to continue the insulin drip until the anion gap has "closed" (i.e., returned to a normal gap of 7 to 12 mmol/L). Premature discontinuation of insulin will lead to worsening acidosis. If serum glucose falls to ≤ 250 mg/dL (14 mmol/L) before the anion gap closes, intravenous fluids should be changed to include 5% dextrose. On occasion, 10% dextrose is necessary to maintain blood glucose between 150 and 200 mg/dL. Once dextrose is included in the intravenous fluids, the insulin infusion should be decreased to 0.05 to 0.1 units/kg/h. It may be necessary to decrease the infusion to 2 to 4 units/hour to avoid hypoglycemia.

The acidosis should be monitored every 2 to 4 hours by following the anion gap and serum bicarbonate. Ketones may appear to increase as the β-hydroxybutyrate is converted to acetoacetate as only the latter is detected by the assay. It is more important to follow the anion gap than the ketonemia. As insulin shuts off production of ketoacids and the kidney excretes those already present, the anion gap normalizes and a non-anion-gap metabolic acidosis becomes evident. As the kidney regenerates bicarbonate over 12 to 24 hours, the acidosis resolves. When it is evident that ketoacid production has been suppressed and the bicarbonate is normalizing, the insulin infusion can be discontinued. At least 0.5 hour before stopping the infusion, however, the patient should be given subcutaneous insulin to prevent the recurrence of the acidosis.

Despite significant acidosis, bicarbonate therapy is rarely, if ever, necessary. Even with severe acidemia (pH 7.0 to 7.2), there is no clear evidence supporting the use of bicarbonate therapy. In fact, bicarbonate infusions can be detrimental because they may delay ketoacid metabolism, unmask hypokalemia, and cause intracellular acidosis. Increased bicarbonate drives $PaCO_2$ production while simultaneously inhibiting respiratory drive, the result of which is intracellular acidosis. Bicarbonate therapy can be considered if the pH is < 7 but should be used judiciously.

ELECTROLYTE REPLETION

The majority of patients with DKA have a substantial potassium deficit. If there is no evidence of renal failure and the patient has good urine output (> 60 mL/h), potassium repletion should begin immediately. The target serum potassium is between 4 and 5 mEq/L. If the serum potassium is < 3.3 mEq/L, insulin should be held and 40 mEq/L/hr of potassium chloride given intravenously until the potassium is above this cutoff. If the potassium falls between 3.3 and 5.5 mEq/L, intravenous fluids should be supplemented with 20 to 30 mEq/L of potassium in order to achieve a serum potassium of 4 to 5 mEq/L. Hold potassium supplementation for K ≥ 5.5.

Routine phosphate repletion is not necessary, as randomized trials failed to show benefit. On the other hand, severe hypophosphatemia (< 1 mg/dL) can have deleterious consequences such as respiratory muscle weakness and rhabdomyolysis. There is also a theoretic risk that depletion of 2,3-diphosphoglycerate will result in a leftward shift of the hemoglobin dissociation curve and impaired oxygen delivery (see Figure A.1 in Appendix A). If phosphate is administered, this should be accomplished by giving one third of the potassium replacement as potassium phosphate. Calcium levels must be monitored closely, as phosphate infusions can precipitate hypocalcemia.

Hyperglycemic Hyperosmolar State

Hyperglycemic hyperosmolar syndrome (HHS), previously known as hyperglycemic hyperosmolar nonketotic state (HHNK), is on the same continuum as DKA with similar pathogenesis. Insulin deficiency combined with glucagon excess results in hyperglycemia. In contrast to DKA, acidosis is mild or completely absent (Figure 82.4). It is postulated that the presence of insulin, even in small amounts, suppresses ketoacid synthesis. Thus, HHS occurs in patients with type 2 diabetes who maintain some degree of endogenous insulin production. However, it is worth noting that studies of insulin levels have failed to substantiate a difference between type 1 and type 2 diabetes. Because ketosis and associated symptoms such as nausea, vomiting, and abdominal pain are absent, patients with HHS tend to present later in the course of their illness than patients with DKA.

Hyperglycemia initiates a cascade of events that results in volume depletion and hyperosmolality, both of which can be quite severe. As the filtered load of glucose rises, the reabsorptive threshold in the renal tubule is surpassed, resulting in glucosuria and a concomitant osmotic diuresis. The hypotonic fluid that is lost contains water, sodium, and potassium. If the patient maintains adequate volume intake, renal function is preserved and glucose excretion continues. In this scenario, serum glucose levels can be maintained at ≤ 400 mg/dL. When volume intake is inadequate, however, GFR and glucose excretion decrease, resulting in a greater degree of hyperglycemia (blood glucose > 600 mg/dL) and more significant volume depletion (see Figure 82.4). The loss of hypotonic fluid combines with the hyperglycemia to produce severe hypertonicity, usually > 320 mOsm/kg of H_2O. Serum tonicity (or effective osmolality) includes osmotically active solutes that do not freely cross cellular membranes:

$$\text{Serum tonicity} = 2[Na^+] + [\text{glucose}]/18 \qquad \text{(Equation 1)}$$

where Na^+ is the serum sodium concentration in mEq/L and glucose is the serum glucose concentration in g/dL with 18 representing the molecular weight of glucose adjusted for different units (g/dL to mOsm/L). Urea nitrogen is not included in this equation because it freely crosses cell membranes and therefore is not an effective osmole. However, urea is included in the formula for calculated serum osmolality when one is determining an osmolar gap.

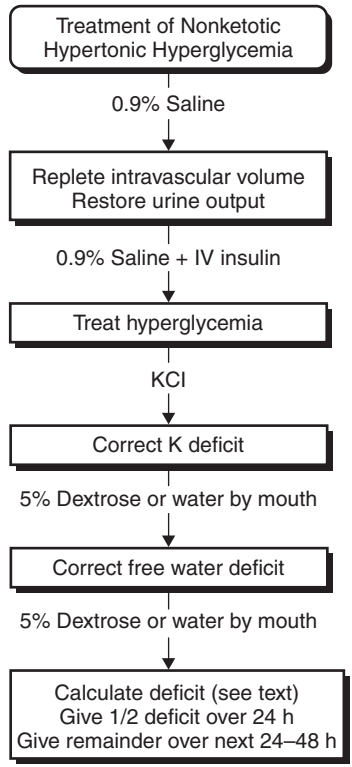


Figure 82.4 Schematic diagram illustrating the pathogenesis of hyperglycemic hyperosmolar state (HHS).

EVALUATION

Patients with HHS universally present with signs and symptoms of volume depletion and hypertonicity. In addition, there may be central nervous system (CNS) symptoms related to hypertonicity, ranging from mild confusion and agitation to seizures and coma. There is a predictable relationship between change in mental status and hypertonicity. Coma is unusual unless serum tonicity is > 340 mOsm/kg of H_2O.

Laboratory analysis (see Table 82.1) usually reveals a glucose concentration greater than 600 mg/dL. Glucose is an effective osmole, "pulling" water out of the intracellular compartment resulting in a diluted serum sodium concentration. Thus, the measured serum sodium concentration can be quite variable, but a normal or high sodium suggests a profound water deficit. To account for this phenomenon of "dilution," the sodium concentration must be corrected for the severity of hyperglycemia (see Equation 2).

Total body potassium depletion is also common in HHS because the osmotic diuresis causes obligate potassium excretion. The serum potassium, however, is often artificially elevated because insulin levels are inadequate to drive potassium into cells. Hypokalemia itself can further inhibit insulin secretion, exacerbating the discrepancy between serum potassium and actual potassium stores.

A mild anion gap metabolic acidosis may also be present due to ketoacidosis or increased lactate production as a consequence of poor organ perfusion. Prerenal physiology is common, marked by an elevated blood urea nitrogen and creatinine. Likewise, the blood urea nitrogen:creatinine ratio is frequently greater than the upper limit of normal, which is 20. If volume contraction is severe enough, acute renal failure may occur.

A thorough history and physical examination are necessary to define precipitating events, although as many as 50% of patients presenting with HHS will not have been previously diagnosed with diabetes. The medical evaluation should screen for infections, myocardial infarction, and other precipitating events. Drugs such as corticosteroids, cimetidine, beta-adrenergic blockers, diuretics, and phenytoin can also precipitate HHS.

TREATMENT

Volume Resuscitation

The therapy of HHS is outlined in Figure 82.3. Most patients with HHS require between 4 and 6 L of saline—substantially more volume than is required for DKA. If the patient is hypotensive, 1 to 2 L of 0.9% saline should be given as an intravenous bolus—for example, 15 mL/kg predicted body weight (PBW; see the footnote to Table 73.4 in Chapter 73 for formulas for PBWs) rounded to the closest 250 mL infused over 20 to 30 minutes. The bolus should be repeated as needed based on the clinical assessment of volume status. Intravenous 0.9% saline should be continued at a rate of 4 to 14 mL/kg/h until intravascular volume is repleted as confirmed by blood pressure and urine output. As with DKA, it is important to reassess volume status repeatedly to avoid iatrogenic volume overload. Patients with end stage renal disease cannot have the glycosuria-induced osmotic diuresis so they do not have the same volume deficit as other patients with HHS and therefore the volume resuscitation should be adjusted accordingly.

Reversal of Hyperglycemia

Volume repletion by itself frequently lowers the serum glucose by as much as 50% as renal perfusion and GFR improve, facilitating glucose excretion. As noted earlier for the treatment steps in DKA, premature use of insulin can result in vascular collapse as glucose and water move out of the extracellular compartment and into the intracellular space. After volume repletion is confirmed, regular insulin should be given as an intravenous bolus of 0.15 U/kg. Although a maintenance insulin infusion at 0.1 U/kg/hour is most convenient, it is not mandatory. This therapy should lower the glucose by 50 to 70 mg/dL/hour, during which time glucose concentration should be monitored frequently.

Hypertonicity

Once the volume contraction is corrected, therapeutic attention should be turned to the hypertonicity. As hyperglycemia is corrected, hypertonicity will improve. The sizable free water deficit that is typically present must also be addressed in order to completely correct hypertonicity. At first glance, the free water deficit may not be evident because hyperglycemia "pulls" water out of the intracellular space, diluting the measured serum sodium concentration. The "corrected" serum sodium takes into account hyperglycemia-induced shifts in water between the intracellular and extracellular compartments:

$$\text{For every 100 mg/dL of glucose greater than 100 mg/dL, one should decrease the serum sodium by} \sim 1.6 \text{ mEq/L} \qquad \text{(Equation 2)}$$

Therefore, a normal or elevated serum sodium concentration implies significant underlying hypernatremia. To estimate the amount of free water necessary to replete this deficit, serum sodium should be corrected for the hyperglycemia. For example, if the uncorrected serum sodium is 140 mEq/L and the serum glucose is 1000 mg/dL, the corrected sodium would be 154 mEq/L (= 1.6 × 9 + 140). Once this is calculated, the free water deficit can be estimated by the following equation:

$$\text{Free Water Deficit} = \text{Total Body Water} \times \{(\text{current } [Na^+] - \text{normal } [Na^+])/\text{normal } [Na^+]\} \qquad \text{(Equation 3)}$$

where [Na^+] is the corrected serum sodium concentration, normal total body water equals 60% of body weight for men and 50% of body weight for women, and normal [Na^+] = 140 mEq/L. For example, if a woman who weighs 60 kg has a corrected serum sodium of 154 mEq/L, her free water deficit = 0.5 × 60 kg × {(154 − 140)/140} = 3 L.

Despite being based on several inaccurate assumptions, this formula provides a fairly good approximation of the underlying water deficit. One half of the calculated free water deficit plus any ongoing losses should be replaced over the first 24 hours and the remainder over the next 48 hours. More rapid correction of the hypernatremia is dangerous and can result in cerebral edema. During periods of hypertonicity, brain cells synthesize idiogenic osmoles to prevent shrinkage. If the water deficit is corrected too quickly, the idiogenic osmoles pull water into brain cells, causing cerebral edema (see Chapter 83).

Electrolyte Repletion

Finally, attention should be paid to correcting the potassium deficit. As soon as urine output is established, potassium repletion can be initiated. Potassium deficits may be as high as 500 mEq. Potassium supplementation can be given orally or intravenously over several days.

COMPLICATIONS

Complications of HHS are usually related to treatment. As discussed earlier, premature administration of insulin may cause vascular collapse. Overzealous correction of the hypertonicity can result in cerebral edema. In addition, an increased risk of thrombotic events has been noted. This hypercoagulability is most likely secondary to volume contraction and endothelial dysfunction. Deep venous thrombosis prophylaxis is therefore recommended.

Alcoholic Ketoacidosis

Alcoholic ketoacidosis (AKA) is an increasingly recognized cause of ketoacidosis in patients with a history of heavy alcohol abuse. The diagnosis is often missed due to the presence of mixed acid-base disorders, including concurrent respiratory and metabolic alkalosis, which are common in alcoholics. With appropriate and timely treatment, AKA resolves quickly without long-term sequelae.

DIAGNOSIS

Alcoholic ketoacidosis occurs in chronic alcohol abusers who present with an anion gap acidosis and ketonemia, but without significant hyperglycemia. Classically, patients report a history of an alcohol binge several days prior, followed by the onset of nausea, vomiting, and abdominal pain. Patients usually present 24 to 48 hours after the onset of gastrointestinal symptoms, at which time the blood alcohol level is usually unmeasurable or present at nonintoxicating levels.

The pathophysiology of AKA has not been clearly defined. The key components are alcohol intake and starvation (Figure 82.5). Starvation leads to decreased glycogen stores, decreased levels of insulin, and increased levels of glucagon. Similar to DKA, there is an increase in fatty acid oxidation and ketone generation. The ratio of β-hydroxybutyrate to acetoacetate is often > 7:1, considerably higher than in DKA. This is driven by the metabolism of alcohol to acetaldehyde via alcohol dehydrogenase that, in turn, converts the coenzyme NAD+ (nicotinamide adenine dinucleotide, oxidized form) to NADH (NAD reduced form). The resulting elevated ratio of NADH to NAD+ favors the generation of β-hydroxybutyrate.

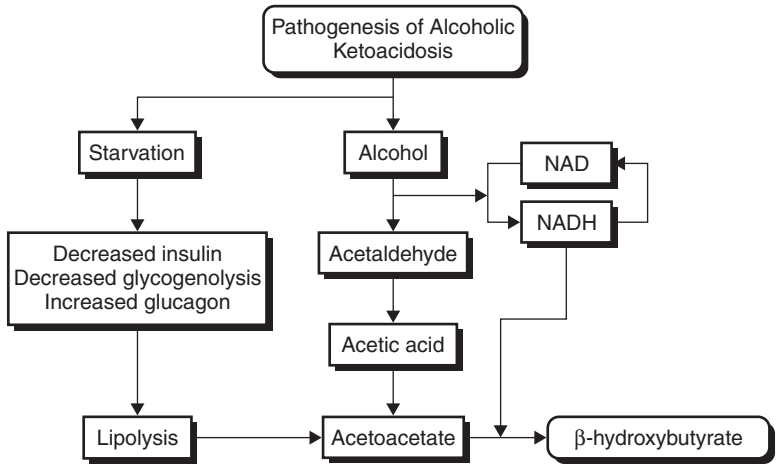


Figure 82.5 Schematic diagram illustrating the pathogenesis of alcoholic ketoacidosis (AKA). NAD, nicotinamide-adenine dinucleotide; NADH, nicotinamide-adenine dinucleotide (reduced form).

EVALUATION

Evaluation of the patient with suspected AKA should include a thorough history and physical examination. Fever is uncommon in AKA unless there is an underlying infection or evidence of alcohol withdrawal. Abdominal pain is commonly present but the abdominal examination is usually benign. If the examination has localizing features, additional workup is warranted.

The laboratory analysis (see Table 82.1) in AKA usually reveals an anion gap metabolic acidosis. The pH, however, may be normal or elevated because patients with AKA frequently have a concomitant respiratory alkalosis due to hyperventilation, as well as a metabolic alkalosis from vomiting. Initially, ketones may not be detected in the serum or urine because the high NADH:NAD ratio favors a shift of acetoacetate to β-hydroxybutyrate. If ketone levels are normal, serum lactate should be measured to rule out lactic acidosis, and a toxicology screen should be performed for ethylene glycol and methanol (see Chapter 57). Although the elevated NADH:NAD ratio also favors the conversion of pyruvate to lactate, alternate sources of lactic acidosis must be sought.

Serum potassium levels may be normal on presentation, but total body potassium depletion is common. Other electrolyte abnormalities include hypophosphatemia and hypomagnesemia. The glucose concentration is normal or low if glycogen stores have been consumed. Approximately 10% of patients with AKA have a glucose level > 250 mg/dL (14 mmol/L), making it difficult to distinguish these individuals from those with true DKA (Figure 82.E1). A history of alcohol bingeing is suggestive but not diagnostic. Once the acute episode resolves, glucose tolerance should be assessed to definitively rule out diabetes, leaving AKA as the diagnosis of exclusion.

TREATMENT

The treatment of AKA begins with volume repletion using 0.9% saline. Because starvation and lack of glycogen stores are contributing factors to AKA, 5% dextrose should be added to intravenous fluids early on unless the patient is already hyperglycemic. Inclusion of dextrose improves the acidosis by decreasing levels of β-hydroxybutyrate and lactate. However, to avoid precipitation of Wernicke encephalopathy, thiamine must be given before the infusion of dextrose. Insulin is not indicated unless the blood glucose is > 250 mg/dL (14 mmol/L), as endogenous insulin production increases with treatment.

Adult Diabetic Ketoacidosis (DKA)
Treatment Guideline

Primary Diagnositic Criteria

- ✦ Serum Glucose greater than 250 mg/dL
- ✦ Serum Ketone (β-Hydroxybutyric Acid > 2 mMol/L)
- ✦ Anion Gap greater than 14 (*anion gap may be normal if albumin is low)

Additional diagnostic criteria (not always present)

- • Arterial pH less than 7.30
- • Serum bicarbonate less than 15 mMol/L

Calculations

- ▪ Anion Gap (Normal 10–14 mEq/L) = $([Na^+]) - ([Cl^-] + [HCO_3^-])$
- ▪ Corrected Anion Gap (for low serum albumin) = [measured AG + (4 – albumin) × 2.5)]
- ▪ Corrected Na^+ = measured $Na^+ + 1.6 \left[\frac{\text{serum glucose} - 100}{100}\right]$
- ▪ Free Water Deficit = [dosing factor (0.6 male, 0.5 female) × body weight (kg)] × [(serum $Na^+ \div 140$) – 1]

Emergency Department Triage

- • If blood glucose greater than 500 mg/dL (or HHH) or urinalysis is dip positive for ketones → ESI Triage Category Level 2.
- • Initial Stat labs: Glucose, Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Magnesium, CBC w/diff, hepatic profile, Urinalysis and Microscopy, Serum Osmolality, Phosphorus, Albumin, Amylase, Lipase, β-HCG (reproductive age females).
- • Place two peripheral IV lines. In cases of severe electrolyte disturbance or shock, consider central venous access.
- • All patients diagnosed with DKA will be admitted to an ICU.

1. Initiate IV Fluids STAT: IVF should be started in the ED and continued in ICU as needed

- • Estimate intravascular volume status (via BUN/Cr, VS, orthostatic BP, urine output, physical exam, HgB) → to estimate saline requirement.
- • Assess free water deficit using corrected serum Na.

A. Initial Fluid Orders:

I. First correct intravascular fluid volume deficit with normal saline at a rate dependent on severity (being more cautious if cardiac or renal disease)

a) 0.9% NaCl at 1–3 Liters/hr (15–20 mL/kg) over 1 hour

b) Give additional 0.9% NaCl IV rapidly if patient remains volume depleted.

B. While Blood Glucose greater than 250 mg/dL -- Subsequent Fluid Orders:

I. Calculate corrected Na:

a) Corrected Sodium less than 134 mEq/L: continue 0.9% NaCl IV at 250–500 mL/hr until glucose less than 250 mg/dL, or corrected Na greater than 134 mEq/L.

b) Corrected Sodium greater than or equal to 134 mEq/L: continue with 0.45% NaCl IV at 250–500 mL/hour until glucose less than 250 mg/dL, or corrected Na less than 134 mEq/L.

II. If corrected Na decreases more than 2 mEq per hour, consider slowing the infusion rate.

Figure 82.E1 Sample protocol for management of diabetic ketoacidosis (DKA). *(Figure created by Cassandra Bellamy, Joan Kinnery, Patricia Heines, and Barry Fuchs. Courtesy of the University of Pennsylvania Health System.)*

C. WHEN Blood Glucose less than 250 mg/dL -- Subsequent Fluid Orders:

I. Calculate corrected Na:

a) Corrected sodium less than134 mEq/L: D5W/0.9% NaCl IV at 100–200 mL/hr

b) Corrected Sodium greater than or equal to 134 mEq/L: D5W/0.45% NaCl IV at 100–200 mL/hr

2. Insulin Administration:

- Hold all home anti-diabetic medications.
- Initiate Insulin therapy **AFTER** IV fluid resuscitation has begun (500 mL or greater) and when potassium is 3.2 mEq/L or greater.
- Insulin Infusion starting dose: (See Step 1 in Insulin Infusion Protocol; Page 4)

A. Blood Glucose greater than or equal to 300 mg/dL → give 0.1 U/kg IV bolus and begin insulin infusion at 0.1 U/kg/hour, rounded to 0.5 U increment, and use Insulin Infusion Protocol.

B. Blood Glucose less than 300 mg/dL → begin insulin infusion at 0.05 U/kg/hour, rounded to 0.5 U increment, and follow Insulin Infusion Protocol.

3. Look for DKA Precipitant

- If clinically indicated consider: Cardiac Enzymes, Blood Cultures, Urine Culture, CXR, EKG Serum lactate.

4. Metabolic Monitoring

- Check POC Blood Glucose on arrival to ICU and repeat every 30–60 minutes while on continuous insulin infusion. For detailed POC glucose monitoring see Insulin Infusion Protocol (Page 3).
- Order STAT basic metabolic panel/BMP (Glucose, Sodium, Potassium, Chloride, CO_2, BUN, Creatinine) every 2–4 hours depending on disease severity and clinical response to treatment.
- Calculate anion gap and corrected serum Na^+ with every basic metabolic panel.

Refractory Metabolic Acidosis:
If pH less than 6.9 (due primarily to metabolic acidosis) despite at least a 1 hour infusion of insulin, consider treatment with IV Sodium Bicarbonate.

5. Potassium (K^+) Correction:

- Per UPHS formulary, maximum peripheral IV infusion rate of Potassium Chloride is 10 mEq/hr. Maximum central IV infusion rate of Potassium Chloride is 20 mEq/hr.
- If serum K^+ is less than 2.8 mEq/L, consider a central line to enable Potassium Chloride infusion rates of 20 mEq/hr. Monitor K^+ every 2 hours until serum K^+ is greater than 2.8 mEq/L.
- If serum K^+ is 2.8 mEq/L or greater use table for suggested repletion regimen. Note suggested repletion assumes normal renal function.
- If oliguria or kidney injury is present, re-check K^+ every 2 hours. If patient does not have oliguria or kidney injury re-check serum K^+ every 4 hours.
- For patients able to tolerate clear liquids by mouth, oral K^+ repletion should be considered.

Serum potassium	Suggested Repletion Regimen
2.8–3.2 mEq/L	administer 60 mEq of Potassium Chloride IV
3.3–3.5 mEq/L	administer 40 mEq of Potassium Chloride IV
3.6–4.9 mEq/L	administer 20 mEq of Potassium Chloride IV
greater than 4.9 mEq/L	No repletion

Figure 82.E1, cont'd.

Diabetic Ketoacidosis (DKA) Insulin Infusion Protocol

Patient Weight = _____ kg

*Anion Gap = ($[Na^+]$) – ($[Cl^-]$ + $[HCO_3^-]$), as measured on a basic metabolic panel

*Correct Anion Gap for low albumin. Corrected anion gap = Measured anion gap + (4 – albumin) × 2.5

Step 1. Initial Insulin Infusion Dosing

- **If Blood Glucose is greater than or equal to 300 mg/dL:** Give 0.1 U/kg IV insulin bolus. Start insulin infusion rate at 0.1 U/kg/hour and round to 0.5 U increment. (Example: weight = 70 kg, 70 × 0.10 = 7; infusion rate is 7 U/hour)
- **If Blood Glucose is less than 300 mg/dL:** Start insulin infusion rate at 0.05 U/kg/hour and round to 0.5 unit increment (Example: weight = 71 kg, 71 × 0.05 = 3.55; infusion rate is 3.5 U/hour)
- Titrate Insulin infusion using Table 1 below. Continue to round dose to the nearest 0.5 U/hour
- **TARGET GOAL: drop in serum glucose is 50–100 mg/dL/hour**
- When Blood Glucose less than or equal to 250 mg/dL go to Step 2

Table 1 – Insulin Infusion Titration for BG greater than 250 mg/dL (NOT on D5 containing fluid)

Blood Glucose Change	Insulin Infusion	POC Glucose Monitoring
Decrease less than 50 mg/dL	Increase rate by 50% (current rate × 1.5)	Repeat blood glucose in 1 hour
Decrease 50–100mg/dL	Continue current rate	
Decrease greater than 100 mg/dL	Decrease rate by 25% (current rate × 0.75)	
Hypoglycemia Treatment		
Less than or equal to 80 mg/dL	➢ HOLD insulin infusion ➢ **Notify MD/NP/PA** ➢ Give 25 mL D50 IVP ➢ **Add D5 containing fluids** ➢ When BG ≥100 mg/dL restart insulin infusion at 0.05 U/kg/hour or continue current rate if already less than 0.05 U/kg/hour ➢ Subsequent infusion titration per Table 2	Repeat blood glucose in 30 minutes

Step 2. Subsequent Insulin Infusion Dosing:

- **When blood glucose is less than or equal to 250 mg/dL, contact MD/NP/PA for order to change of insulin infusion rate to 0.05 U/kg/ hour OR continue current rate if already equal to or less than 0.05 U/kg/hour**
- **Contact MD/NP/PA for an order for dextrose containing IV fluids: Usual rate is 100–200 mL/hr**
- Titrate Insulin infusion using Table 2 below. Continue to round dose to the nearest 0.5 U/hour
- **TARGET GOAL: Keep Blood Glucose between 150–200 mg/dL until corrected anion gap is less than 14 for two consecutive measurements**
- **Notify MD/NP/PA** if two consecutive rate increases are required

Figure 82.E1, cont'd.

Table 2 – Subsequent Insulin Infusion (ON D5 CONTAINING FLUID)		
Blood Glucose	**Insulin Infusion**	**POC Glucose Monitoring**
Greater than 250 mg/dL	Increase rate 50% (current rate × 1.5)	Repeat blood glucose in 1 hour
201–250 mg/dL	Increase rate 25% (current rate × 1.25)	
150–200 mg/dL	Continue current rate	
80–149 mg/dL	Decrease rate 50% (current rate × 0.5)	
Less than or equal to 80 mg/dL	➢ HOLD insulin infusion ➢ **Notify MD/NP/PA** ➢ Give 25 mL D50 IVP ➢ Restart at 25% of previous rate (current rate × 0.25) when Blood Glucose greater than 99 mg/dL	Repeat blood glucose in 30 minutes

Figure 82.E1, cont'd.

6. Transition from IV to Subcutaneous Insulin (SQ)

A. When to transition:

- Three requirements should be met before you transition to SQ Insulin:
  1. The anion gap has normalized in 2 consecutive blood samples (greater than 14 when corrected for albumin).
  2. The glucose values are within target of 150–200 mg/dL and insulin requirements are stable.
  3. The patient is alert and able to tolerate clear liquids. Note full dietary intake is not required when above requirements are met.

B. Dosage and Type of Insulin to administer:

Definition: Total Daily Dose of Insulin (TDD) = estimated number of units of all types of insulin to be given in 24 hours, e.g., aspart (prandial and correction factor) plus glargine (Lantus)

1. Calculate the estimated Total Daily Dose (TDD)

A. Patient receiving outpatient insulin therapy: Estimated TDD is equal to the sum of all insulin types prescribed in outpatient insulin regimen.

~OR~

B. Patient NOT previously on insulin therapy: Estimated TDD is equal to 0.5 U/kg/day.

2. Compare the estimated TDD to current intravenous insulin therapy:
(Current hourly insulin infusion rate × 24 hours = 24 hour IV insulin requirement)

A. If estimated TDD is **less than** current 24 hour intravenous insulin requirement then use the average of the estimated TDD and 24 hour intravenous insulin requirement as the "Acute" TDD to calculate subcutaneous regimen.

{(TDD + 24 hour intravenous insulin requirement) ÷ 2 = Average TDD}

B. If estimated TDD is **greater than** current 24 hour intravenous insulin requirement then use the lesser TDD value to calculate subcutaneous regimen (consider a diabetes management consult).

3. Dosing and type of Insulin:

A. Administer 50% of the TDD calculated from above as long acting Insulin, given once daily (basal, insulin glargine) and administer 50% of the TDD calculated from above as rapid acting Insulin (aspart), usually divided 3 times daily, administered with meals (prandial).

B. GIVE THE LONG ACTING SUBCUTANEOUS INSULIN (INSULIN GLARGINE) **2 HOURS PRIOR** TO DISCONTINUING IV INSULIN INFUSION.

C. Order Correction factor subcutaneous insulin, blood glucose monitoring and hypoglycemia protocol.

4. Important Caveats:

- The instructions given above are based on consensus recommendations considering general populations of patients
- Individual inpatient requirements for insulin may vary significantly:
  - For patients taking insulin at home, the adequacy of glucose control at baseline will have an impact on transition efficacy.
  - In all patients with DKA or HHS, any unresolved precipitant may result in an underestimation of the total insulin requirement (this would be reflected in the amount of insulin required in the prior 1–2 hours vs. the estimated value based on weight).
- In all patients with resolving DKA or HHS, glucose and metabolic panels should be carefully monitored to determine the optimal insulin regimen needed to obtain adequate glucose control
- The Diabetes Management Service, available through consult pager, can address questions regarding insulin transition dosing or any other ongoing diabetes management issues.

Figure 82.E1, cont'd.

Attention should also be directed at correcting underlying electrolyte abnormalities. Potassium replacement is often necessary and can be given intravenously or orally if tolerated. Hypophosphatemia < 1 mg/dL (0.32 mmol/L) should be treated with potassium phosphate. Hypomagnesemia is also routinely treated, although data regarding the efficacy of this approach are limited.

Finally, because these patients are at high risk for the development of alcohol withdrawal syndrome, empirical use of benzodiazepines for prophylaxis can be considered (see Chapter 31). Mortality attributable to AKA is rare. When it occurs, death is usually due to delayed treatment, comorbid disease, or alcohol withdrawal syndrome.

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CHAPTER 83

Metabolic Acidoses and Alkaloses

Stanley Goldfarb ■ James B. Reilly

Acid-base disturbances are common in patients admitted to the intensive care unit (ICU) and can cause widespread, clinically important physiologic changes. Anticipating and accounting for these changes, and adjusting to the physiologic consequences as these derangements resolve, are essential to the management of critically ill patients. This chapter briefly outlines the terminology, physiology, diagnosis, and management of acid-base disorders commonly encountered in the ICU.

Acidosis and *alkalosis* refer to the pathophysiologic processes that cause the body to accumulate or lose H^+ ions, whereas *acidemia* and *alkalemia* refer to the actual changes in arterial blood pH. *Metabolic* acid-base disorders primarily affect serum bicarbonate (HCO_3^-) concentration and relate mainly to renal handling of the bicarbonate ion. *Respiratory* acid-base disorders primarily affect $Paco_2$ and relate mainly to respiratory handling of carbon dioxide in the process known as ventilation. The complex interactions of these processes, as well as a complicated system of buffers, are responsible for maintaining body pH within a narrow physiologic range.

Physiology and Pathophysiology

ACID-BASE PHYSIOLOGY

Metabolism of food ultimately produces acid (H^+) and base (HCO_3^-). A typical American diet, heavy in protein, produces slightly more acid than base, equal to approximately 1 mmol H^+ per kg body weight per day; in contrast, a strict vegetarian diet produces a net base. Basic organic anions—for example, citrate and acetate—should be considered equivalent to HCO_3^- because they produce HCO_3^- when oxidized. Complete oxidation of carbon-containing compounds yields the volatile acid, carbonic acid (H_2CO_3), as shown by Equation 1:

$$H^+ + HCO_3^- \Leftrightarrow H_2CO_3 \Leftrightarrow CO_2 + H_2O \qquad \text{(Equation 1)}$$

The effect of these metabolic events on acid-base homeostasis is influenced by respiration and the exhalation of CO_2. Nonvolatile organic acids (e.g., lactic, beta-hydroxybutyric, and acetoacetic acids) are acids produced by incomplete oxidation and do not yield carbon dioxide. The H^+ from nonvolatile acids (e.g., sulfuric and lactic acids) must be excreted by the kidneys, as CO_2 is not produced in these reactions.

Buffers minimize pH changes that result from the addition or removal of H^+. Equation 1 can be rewritten in the Henderson-Hasselbalch format,

$$pH = pK + \log[HCO_3^-]/[CO_2] \qquad \text{(Equation 2)}$$

where pK = 6.1 (equilibrium constant for carbonic acid), $[HCO_3^-]$ = concentration (mmol/L) of bicarbonate ion, and $[CO_2]$ is the concentration (mmol/L) of CO_2 dissolved in blood. $[CO_2]$ is determined by measuring $Paco_2$ and multiplying it by the solubility coefficient (0.03 mm Hg/mmol/L). Thus, a normal $Paco_2$ of 40 mm Hg is equal to 1.2 mmol/L of CO_2. When $Paco_2$

is 40 mm and $[HCO_3^-]$ is also normal (i.e., 24 mmol/L), the ratio of $[HCO_3^-]/[CO_2]$ equals 20:1 (and log 20 = 1.3). This ratio corresponds to the normal pH of 6.1 + 1.3 or 7.40. Remember that it is the ratio of bicarbonate to carbon dioxide in the blood that determines pH—not the absolute value of either.

The $[HCO_3^-]/[CO_2]$ buffer pair is the most important because of the abundance of each part's components and how the relationship between them can be influenced independently by the kidneys and lungs. For example, by Equation 1, in metabolic acidosis, the addition of H^+ increases the concentration of hydrogen ion, $[H^+]$ (which, at equilibrium, proportionately decreases the concentration of bicarbonate ion $[HCO_3^-]$). By the law of mass action, the increased $[H^+]$ drives the reaction to the right, increasing the production of CO_2.

Under normal conditions, this increased CO_2 production does not raise $[CO_2]$ or $Paco_2$ because of a compensatory increase in ventilation. Without this increased ventilation, there would be no attenuation of the fall in pH caused by the metabolic acidosis. In addition to buffering by $[HCO_3^-]/[CO_2]$, inorganic phosphates (especially those in bone), plasma and intracellular proteins (such as albumin), and hemoglobin all help to buffer changes in pH. These secondary buffer systems do contribute some to maintenance of normal extracellular and intracellular pH, but diagnosis and management of acutely ill patients in the ICU depends mainly on the $[HCO_3^-]/[CO_2]$ system. Therefore, this will be the primary focus of this chapter.

RENAL ACID-BASE HANDLING

Normally functioning kidneys regulate the serum HCO_3^- concentration in two ways. First, they reabsorb the filtered load of HCO_3^- (= GFR × serum $[HCO_3^-]$). Losing 1 mmol of HCO_3^- in the urine would be equivalent to gaining 1 mmol of H^+. Second, the kidneys excrete H^+ at a rate equal to the metabolic production of H^+ and restore the HCO_3^- consumed in buffering. HCO_3^- reabsorption occurs in the proximal tubule by a mechanism that depends on carbonic anhydrase to accelerate the hydration reaction of CO_2 (Equation 1, with the reaction arrows going right to left). The diuretic acetazolamide inhibits carbonic anhydrase, to increase bicarbonaturia (renal "dumping" of bicarbonate) and often results in metabolic acidosis.

H^+ is excreted by the distal nephron, stimulated by distal Na^+ delivery and aldosterone. Effective excretion of H^+ depends mainly on the urinary buffers phosphate and ammonia. Urinary phosphate excretion is generally fixed and depends on dietary intake, whereas urinary ammonia, produced by renal metabolism of the amino acid glutamine, varies according to physiologic needs. Ammonia production is stimulated by metabolic acidosis, hypokalemia, and glucocorticoids and, conversely, is suppressed by metabolic alkalosis, hyperkalemia, and glucocorticoid deficiency. These mechanisms are effective for removing the daily ingested acid load and are also the primary compensation mechanisms used to maintain pH in the face of both metabolic and respiratory acidoses.

COMPENSATORY MECHANISMS

After the onset of a primary acid-base disturbance, compensation mechanisms return blood pH toward normal values. Under most circumstances, primary metabolic abnormalities induce changes in ventilation, and renal acid-base handling changes in response to primary respiratory abnormalities. Although a compensatory process tends to normalize blood pH, it rarely, if ever, returns pH to 7.40. Therefore, the serum pH ultimately reflects which process is the primary disturbance and which is simply compensatory (see the acid-base nomogram [Figure D1] in Appendix D).

Respiratory Compensation for Metabolic Disorders

The respiratory response to acute metabolic acid-base disturbances begins immediately. Hyperventilation compensates for metabolic acidosis, typically characterized by increasing tidal volume,

although tachypnea can occur. This pattern can be subtle, but in its most pronounced form it is referred to as Kussmaul breathing/respiration. The magnitude of the compensation varies with the degree of acidosis but can be accurately predicted by "Winter's formula" for acute metabolic acidosis,

$$\text{Paco}_2 \text{ (predicted) (mm Hg)} = 1.5 \text{ (mm Hg/mmol/L)} \times [\text{HCO}_3^-] \text{ (measured by ABG) (mmol/L)} + 8\ (\pm 2) \text{ (mmol/L)} \quad \text{(Equation 3)}$$

where Paco_2 (predicted) is the Paco_2 level expected only from respiratory compensation, and $[\text{HCO}_3^-]$ (measured) is the value obtained from an arterial blood gas (ABG) (in which the $[\text{HCO}_3^-]$ is calculated by Equation 2 in Chapter 84 (the Henderson-Hasselbalch equation) from the measured parameters of pH and Paco_2)

Hypoventilation with elevation of Pco_2 compensates for metabolic alkalosis, proportionate to the alkalosis. However, the hypoventilatory response is more variable than the hyperventilatory response and may be limited by hypoxemia as ventilation slows. Consequently, the compensatory Paco_2 is often difficult to predict accurately. The acid-base map or nomogram in Appendix D limits compensatory elevation of Paco_2 to 55 mm Hg.

Renal Compensation for Respiratory Disorders

Respiratory acid-base disorders elicit metabolic (renal) compensation. In compensation for respiratory alkalosis, the serum $[\text{HCO}_3^-]$ decreases 2 to 4 mEq/L for each 10 mm Hg decrease in the Paco_2 and the process takes 12 to 24 hours to complete. The serum $[\text{HCO}_3^-]$ rises in compensation for respiratory acidosis; it takes 3 to 5 days to achieve a 1 to 3 mEq/L increase for every 10 mm Hg rise in Paco_2.

Metabolic Acidosis

Metabolic acidoses occur when the rate of nonvolatile acid intake (or production), or HCO_3^- loss, exceeds the rate of renal H^+ excretion and, therefore, HCO_3^- production by the kidney. A conventional distinction exists between processes that cause an increase in the anion gap and processes that do not.

THE ANION GAP AND ELEVATED GAP ACIDOSES

The anion gap (expressed in mEq/L) is the difference between measured serum cations and anions, as in Equation 4,

$$\text{Anion gap} = [\text{Na}^+] - \{[\text{Cl}^-] + [\text{HCO}_3^-]\} \quad \text{(Equation 4)}$$

where $[\text{HCO}_3^-]$ is the (total) serum bicarbonate (= dissolved CO_2 and HCO_3^-) as measured on a venous blood sample as part of the same chemistry panel giving values (mEq/L) for serum $[\text{Na}^+]$ and $[\text{Cl}^-]$. The anion gap consists of net negatively charged proteins (albumin is the major contributor) and small anions like urate and phosphate. The normal anion gap ranges from 8 to 12 and increases when nonvolatile acids accumulate because of increased net production (e.g., lactate, acetoacetate, or beta-hydroxybutyrate) or decreased renal excretion (e.g., phosphate and sulfate in chronic renal failure).

Hypoalbuminemia decreases the anion gap. In general, a decrease in albumin concentration of 1 mg/dL will decrease the normal anion gap by approximately 2.5 mEq/L. Paraproteinemias can increase or decrease the gap depending on the charge of the paraprotein. By increasing the net negative charge of albumin, alkalemia widens the gap; acidemia has the opposite effect, and as a result, the anion gap is an underestimate in significant acidemia. Renal disease causes both an anion gap and a normal gap acidosis (Tables 83.1 and 83.2).

Lactic acidosis and diabetic ketoacidosis (DKA) commonly cause an anion gap acidosis in ICU patients (see Table 83.1). In DKA, metabolism of fatty acids produces H^+ and the anion acetoacetate. Starvation produces ketosis but only minimal acidosis. In contrast, alcoholic ketoacidosis (AKA), which includes aspects of starvation, can produce a severe anion gap acidosis. Binge drinking leads to an altered redox state that generates the anion beta-hydroxybutyrate (which is not detected by the nitroprusside reaction for ketones, unlike acetoacetate).

Several other toxins induce anion gap acidoses. Salicylates induce lactic acid production while also stimulating respiratory centers to produce a second primary disorder, a respiratory alkalosis. Methanol and ethylene glycol are metabolized by hepatic alcohol dehydrogenase to various toxic metabolites, some of which also elevate the anion gap. Particularly, metabolism of methanol produces the toxins formaldehyde and formic acid. Metabolism of ethylene glycol produces glycolic and oxalic acids. In acute acetaminophen toxicity, glutathione depletion can result in elevated concentrations of gamma-glutamyl cysteine, leading to accumulation of pyroglutamic acid. Suspect acetaminophen toxicity in patients with a large anion gap, hepatic or renal dysfunction, and a negative preliminary toxicologic screen for methanol or ethylene glycol. Inhalation of toluene, a component of paint thinners and many glues, produces an anion gap acidosis via metabolism to hippuric acid. Renal failure leads to an accumulation of phosphate and sulfate, elevating the anion gap, most often late in the disease.

TABLE 83.1 ■ **Metabolic Acidoses: Anion Gap Acidoses**

Type of Anion	Etiology
Ketones	Diabetic ketoacidosis
	Alcoholic ketoacidosis
Toxins, poisons	Salicylates
	Methanol
	Ethylene glycol
	Acetaminophen
Lactate	Lactic acidosis
Phosphates and sulfate	Chronic renal failure

TABLE 83.2 ■ **Metabolic Acidoses: Hyperchloremic (Nonanion Gap) Acidoses**

Mechanism of Disorder	Etiology
Addition of equimolar H^+ and Cl^-	Ingestion or administration of HCl, NH_4Cl, lysine, or arginine HCl
Loss of HCO_3^- with equimolar gain of Cl^-	Secretory diarrhea (cholera-like) caused by infections or laxatives; other gastrointestinal loss of base (pancreatic fistula)
Inability to excrete daily load of H^+	Renal tubular acidosis (see Table 83.3)
	Chronic renal failure
Inability to maintain serum [HCO_3^-] because of renal losses of HCO_3^-	Renal tubular acidosis (see Table 83.3)
	Acetazolamide use
Dilution of serum [HCO_3^-]	Volume expansion with fluid loading with NaCl

NORMAL ANION GAP METABOLIC ACIDOSES

In general, normal gap metabolic acidosis results from either renal or gastrointestinal loss of bicarbonate. An increment in serum [Cl^-] "matches" the decrement in serum HCO_3^-; therefore, these processes are often called "hyperchloremic" metabolic acidoses. For example, ingestion or administration of HCl yields a hyperchloremic acidosis. Intake of the chloride salts of ammonium, arginine, or lysine also causes metabolic acidosis because their metabolism yields HCl. As noted earlier, acidosis from impaired renal H^+ excretion occurs in early renal failure. Other renal disorders can lead to a normal gap metabolic acidosis (Table 83.2). Use of carbonic anhydrase inhibitors like acetazolamide can cause a normal gap metabolic acidosis by inhibiting bicarbonate reabsorption in the proximal tubule.

Renal tubular acidosis (RTA) refers to one of several renal tubular defects, congenital or acquired, that impair either reclamation of filtered HCO_3^- or H^+ excretion (Table 83.3). There are three major types: distal (type I), proximal (type II), and low-renin hypoaldosteronism (type IV). The distal (type I) form can be the most severe, sometimes leading to [HCO_3^-] levels below 10 meq/L. Distal RTA is caused by a defect in H^+ secretion in the collecting tubules, preventing the excretion of the entire daily acid load. Urinary pH is almost always > 5.5. The proximal (type II) form is usually less severe, produced by a defect in HCO_3^- reabsorptive capacity. Because intact distal H^+ secretion can compensate for the proximal loss of bicarbonate, [HCO_3^-] levels rarely reach equilibrium below 14 mEq/L; however, at this point, urinary pH can fall below 5.5. Often proximal RTA is accompanied by hypophosphatemia, hypouricemia, aminoaciduria, and glucosuria, called Fanconi syndrome in combination. Low-renin hypoaldosteronism (type IV RTA) is an aldosterone-deficient (or resistant) state in which hyperkalemia mediates decreased ammonia production, leading to impaired urinary acid excretion. Like proximal RTAs, bicarbonate levels rarely get below 15 mEq/L, and resolution of hyperkalemia often will relieve the acidosis. These

TABLE 83.3 ■ **Categories of Renal Tubular Acidosis**

Category	Description
Proximal RTA (type II)	Defective reabsorption of filtered HCO_3^- by the proximal tubule is frequently associated with glycosuria and aminoaciduria (Fanconi syndrome). It can be inherited or acquired (amphotericin B, renal transplants). Because HCO_3^- is continually excreted, urine pH is often > 5.5, but it can be lower. HCO_3^- administration exaggerates HCO_3^- potassium losses.
Distal RTA (type I)	Limitations in H^+ secretion in the distal nephron results in accumulation of H^+ and severe hyperchloremic metabolic acidosis. Distal RTA can be inherited or acquired (autoimmune diseases or many drugs). It is associated with hypercalciuria, nephrocalcinosis, and nephrolithiasis. The urine pH is always > 5.5.
Low renin hypoaldosteronism (type IV)	Decreased synthesis of ammonia reduces urinary buffer content, decreasing net H^+ excretion. Tubular mechanisms of H^+ secretion, however, are intact and urine pH is frequently < 5.5. Ammonia synthesis is inhibited by hyperkalemia and glucocorticoid deficiency. Some hyperkalemic patients also have low renin hypoaldosteronism (also called type IV RTA). Hyperkalemia in these patients fails to stimulate aldosterone secretion; they also tend to be unresponsive to exogenous aldosterone.

three phenotypes are caused by many different defects, congenital and acquired. A precise diagnosis may not be necessary for management of ICU patients, but recognition of a phenotype may facilitate diagnosis of otherwise unrecognized systemic illnesses or toxic effects.

The most common cause of HCO_3^- loss via the gastrointestinal tract is diarrhea of almost any cause, including infections and, rarely, laxative abuse. Ingestion of anion exchange resins—for example, cholestyramine chloride—causes HCO_3^- loss by exchanging chloride for bicarbonate in the gut, as does the ingestion of calcium- or magnesium-containing laxatives. Though less commonly seen now than in the past, ureteral diversion after ureterosigmoidostomy and ileal conduit results in HCO_3^- loss in the diverted urine, as the sigmoid pouch absorbs chloride through an anion-exchange pump as it secretes bicarbonate into the urine. Further, the colonic pouch can directly absorb urinary ammonium, counteracting the major mechanism of urinary acid excretion. External loss of biliary and pancreatic secretions, like that which occurs after bladder-draining pancreas transplant, also results in net loss of HCO_3^-. Finally, dilution of serum HCO_3^- can occur subsequent to large volumes of NaCl in saline or total parenteral nutrition, and this may result in a normal gap "expansion acidosis." Nonbicarbonate buffers, however, limit the severity.

Metabolic Alkaloses

Excess addition of alkali (e.g., HCO_3^-, lactate, or citrate) or excess excretion or loss of H^+ (via either the gastrointestinal tract or the kidneys) can generate a metabolic alkalosis. In either case, the elevated [HCO_3^-] is maintained because the kidneys fail to excrete it. Several mechanisms can reduce renal HCO_3^- excretion. First, renal failure decreases HCO_3^- excretion because of a decreased glomerular filtration rate. Second, volume depletion also reduces HCO_3^- excretion and increases H^+ excretion. This occurs when angiotensin II stimulates the proximal tubule to increase HCO_3^- reabsorption. Additionally, aldosterone acts to increase H^+ secretion in the distal nephron and also induces hypokalemia, which stimulates ammoniagenesis and further increases H^+ secretion.

Patients with volume depletion and alkalosis are usually depleted of Cl^- and have low urinary [Cl^-] (< 20 mEq/L). Such "chloride-sensitive metabolic alkalosis" is corrected with NaCl or KCl repletion. In other types of metabolic alkaloses, however, the volume status plays no role in pathogenesis and the urine [Cl^-] is normal (> 30 mEq/L). As expected, these patients with a "chloride-resistant metabolic alkalosis" do not improve with NaCl or KCl administration (Table 83.4).

TABLE 83.4 ■ **Metabolic Alkaloses**

Category	*Chloride-Sensitive Alkalosis*		*Chloride-Resistant Alkalosis*	
Urinary [Cl^-]	< 20 mEq/L			> 30 mEq/L
Extracellular fluid volume	Decreased		Increased	Euvolemic or decreased
Site of problem	**Gastrointestinal**	**Renal**	**Renal**	**Renal**
Causes	Vomiting Nasogastric suction Chloride-rich diarrhea Villous adenoma	After chronic hypercapnia Diuretics K^+ depletion (mild-moderate) After organic acidosis Refeeding alkalosis	Excess mineralocorticoid states	Bartter syndrome K^+ depletion (severe) Exogenous HCO_3^- load in presence of renal failure Nonreabsorbable anion

CHLORIDE-SENSITIVE METABOLIC ALKALOSES

Loss of proton-rich gastric secretions, either by vomiting or nasogastric suction, generates an alkalosis. The associated volume depletion maintains the alkalosis, even if vomiting stops or suction is discontinued. Between vomiting episodes, urinary pH remains low, indicating that urinary HCO_3^- is virtually nonexistent. Only administration of saline corrects the alkalosis. A less common gastrointestinal (GI) cause of a metabolic alkalosis is chloride-rich diarrhea. This occurs in congenital chloridorrhea, a rare condition usually diagnosed early in life. Chloride-rich diarrhea is more common in the pediatric population. In adults, it may be caused by viral gastroenteritis or villous adenomas.

Diuretics, particularly thiazides and loop diuretics, are important causes of metabolic alkaloses. The primary mechanism of alkalosis resulting from use of these drugs is by inducing volume depletion, enhancing renal proton excretion by the renin-angiotensin-aldosterone axis, and, secondarily, by inducing hypokalemia and stimulating ammonia production. Repletion of potassium and intravascular volume relieves the alkalosis.

Alkalosis may occur in patients after correction of hypercapnia if they become volume depleted, hypokalemic, or both, because of diuretic therapy. Some antibiotics such as carbenicillin are anions that are not reabsorbed by the kidneys. Their excretion obligates loss of cations like Na^+, K^+, H^+, and ammonium ($NH4^+$). Such antibiotics cause alkalosis when simultaneous NaCl administration is limited for other reasons. Although carbenicillin is rarely used now, a similar phenomenon has been described with ampicillin at high doses.

CHLORIDE-RESISTANT METABOLIC ALKALOSES

The hallmark of chloride-resistant alkalosis is that volume depletion plays no significant role in maintenance of the alkalosis. Alkalosis frequently occurs after resolution of an organic acidosis (e.g., ketoacidosis or lactic acidosis), especially if HCO_3^- was administered during the acidosis. During recovery, metabolism of lactate and ketoacids regenerates HCO_3^- and, if hypovolemia or hypokalemia coexist, the administered HCO_3^- plus the regenerated HCO_3^- can result in severe, prolonged metabolic alkalosis, with all the untoward systemic effects of alkalemia.

Administration of large quantities of organic anions such as citrate (especially in blood transfusions) can have similar effects. Transient "refeeding" alkalosis can follow prolonged starvation because ketoacid anions accumulate during starvation and are then converted to bicarbonate. In renal failure, because HCO_3^- is not excreted, excessive alkali ingestion or administration can lead to severe metabolic alkalosis. In addition, ingestion of large amounts of calcium carbonate can lead to renal failure, metabolic alkalosis, and hypercalcemia, a triad known as *milk-alkali syndrome*.

An alkalosis that does not correct with administration of saline should also make one consider rare syndromes. Mineralocorticoid excess (whether primary or secondary) increases net H^+ excretion directly and also via hypokalemia. These patients are volume expanded rather than volume contracted, and they are often hypertensive. Additionally, several genetic defects exist that induce localized tubular dysfunction, causing alkalosis and hypokalemia. These various defects cause two major phenotypes, known as Gitelman and Bartter syndromes. In Gitelman syndrome, a defect in the distal tubule thiazide-sensitive NaCl channel results in wasting of sodium, chloride, and potassium, but it also causes low urinary calcium, mimicking the actions of thiazide diuretics. Bartter syndrome tends to have less magnesium wasting and more calciuria, mimicking the actions of a loop diuretic. In both of these syndromes, patients have chronically high levels of renin and aldosterone and as such are generally not volume depleted. Both syndromes often present in childhood but there are late presentations, particularly in milder forms of the diseases. Though rare, consider these syndromes in volume replete patients with no obvious bicarbonate load, whether exogenous or endogenous from a resolving organic acidosis.

Respiratory Acidosis and Alkalosis

Be mindful of common causes of primary respiratory acid-base disorders, as abnormalities in the serum bicarbonate concentration are often compensating for a yet unrecognized respiratory disorder.

RESPIRATORY ACIDOSIS

Any respiratory disorder that limits ventilation can lead to a rise in the $Paco_2$ (see Chapter 1 for more mechanistic details). Very severe chronic obstructive lung disease (e.g., FEV_1 < 750 mL) (Chapter 76) and the obesity-hypoventilation syndrome (OHS) (but not uncomplicated obstructive sleep apnea [OSA]; see Chapter 80) can result in chronic hypercapnia. However, other important causes for respiratory acidosis exist in ICU patients. Central nervous system depression, whether medication- or ingestion-induced or caused by organic disease, often suppresses respiratory drive enough to raise $Paco_2$ Additionally, muscle weakness of any cause can lead to a respiratory acidosis. One should consider neuromuscular disorders like myasthenia gravis, which primarily affects the diaphragm, or primary diaphragmatic dysfunction caused by phrenic nerve injury if a more obvious cause is not present (Chapter 67).

RESPIRATORY ALKALOSIS

Hyperventilation for any reason can cause a respiratory alkalosis, and it may be so subtle as to escape clinical detection. Commonly, anxiety and pain cause hyperventilation. Primary lung diseases, such as pulmonary edema, or restrictive diseases, like idiopathic pulmonary fibrosis, are other common causes. Some clinically relevant systemic conditions induce a respiratory alkalosis, such as early sepsis, postulated to be due to subclinical pulmonary edema from cytokine-induced capillary leak. Additionally, cirrhosis and other hepatic failure disorders result in a respiratory alkalosis, which is thought to be related to central hyperventilation caused by excessive circulating progestins. Other notable etiologies in ICU patients include acute or chronic renal failure, pregnancy (Chapter 28), aspirin intoxication (Chapter 57), acute pulmonary embolus (Chapter 77), and, possibly most commonly, inappropriate overventilation induced by use of a mechanical ventilator (see Chapter 2 and Appendix B).

Diagnostic Evaluation

Identifying a primary acid-base disturbance may be difficult, but it is essential to normalizing pH and maintaining necessary physiologic compensatory mechanisms. It is recommended that one start with a basic metabolic panel (BMP, also referred to as a "Panel 7," which measures concentrations of serum sodium, potassium, chloride, total bicarbonate, blood urea nitrogen [BUN], and creatinine) and arterial blood gas (ABG) measurements to evaluate the acid-base status of every critically ill patient.

Because patients can have two or more acid-base disorders at the same time, a systematic approach for diagnosing complex or mixed acid-base disturbances is also recommended. This approach relies on using all available data rather than the *isolated* use of arterial blood gas measurements (with or without an acid-base nomogram; see Appendix D for the latter).

The patient's *history* and *physical examination* are the foundation of the diagnostic approach. First, consider how symptoms (vomiting, diarrhea, and polyuria), medical history (diabetes mellitus, congestive heart failure, and emphysema), medications (diuretics, laxatives, and sedatives), treatments (mechanical ventilation, nasogastric suction, intravenous fluid), and physical observations (signs of extracellular volume contraction or expansion, hypotension, tetany, jaundice, hyperpnea,

morbid obesity, and cyanosis) might be related to acid-base balance. Then review not only the patient's serum and urinary electrolytes and the arterial blood gas measurements but also common tests such as complete blood count, liver and renal function tests, urinalysis, and chest radiograph for the presence of lung or renal disease, to support or refute one's initial impression of the likely acid-base abnormalities to be encountered. After the data-gathering phase, one can formulate a *differential diagnosis* of the particular acid-base disorders (see Tables 83.1 to 83.4).

A systematic approach to interpretation of the arterial blood gas can both confirm a clinical impression and expose an unrecognized disturbance that might change management. To avoid the "satisfaction of search" phenomenon, it is best to evaluate the basic metabolic panel and blood gases systematically. The five-step approach in Table 83.5 is recommended.

In the presence of an anion gap acidosis, controversy exists regarding how to interpret the magnitude of the change in the anion gap compared to the change in bicarbonate levels (the "delta-delta" phenomenon). This relationship is less consistent than believed previously, but it may still be helpful diagnostically in diagnosing a so-called triple disorder (i.e., three different types of primary acid-base disorders present in the same patient). It may no longer be correct to assume that serum bicarbonate will decrease by 1 mEq/L for each 1 mEq/L in elevation of the anion gap. More likely the ratio of $\Delta AG/\Delta[HCO_3]$ is anywhere between 1 and 1.5, depending on the etiology of the acidosis. A reasonable approach might be to consider a normal $\Delta AG/\Delta[HCO_3]$ ratio to be between 1 and 1.5, and a $\Delta AG/\Delta[HCO_3] > 1.5$ consistent with the presence of an additional metabolic alkalosis. Likewise, a $\Delta AG/\Delta[HCO_3] < 1$ is consistent with an additional normal gap ("nongap") metabolic acidosis. Proceed with caution when interpreting the $\Delta AG/\Delta[HCO_3]$ and use it as one piece of clinical information in the total evaluation.

TABLE 83.5 ■ **Five-Step Approach to Diagnosis of Acid-Base Disorders from an Arterial Blood Gases and Plasma Electrolytes**

1. Identify the likely primary process as an acidosis or alkalosis.

The pH is dictated by the primary process

pH < 7.38: acidemia (acidosis is likely primary)

pH > 7.42: alkalemic (alkalosis is likely primary)

2. Is primary process respiratory or metabolic?

If acidemic:

Respiratory acidosis if $Paco_2$ is > 40

Metabolic acidosis if HCO_3 is < 24

If alkalemic:

Respiratory alkalosis if $Paco_2$ is < 40

Metabolic alkalosis if HCO_3 is > 24

3. Respiratory processes: acute or chronic?

Acute: pH change 0.08 for every 10 mm Hg change in the $Paco_2$ from 40

Chronic: pH will change only 0.03 for every 10 mm Hg change in $Paco_2$ from 40

4. Metabolic processes: respiratory compensation can be too much, too little, or "just right!"

Use Winters' formula applied to ABG for the target $Paco_2$: **$Paco_2 = 1.5[HCO_3] + 8 (\pm 2)$**

If actual $Paco_2$ is too high: additional respiratory acidosis

If actual $Paco_2$ is too low: additional respiratory alkalosis

5. Always calculate the anion gap (AG): if there is an elevated anion gap, there is* always *a metabolic acidosis.

$AG = [Na] - ([Cl] + [HCO_3])$; normal range = 8–12

See Table 83.1 for the differential diagnosis.

Other serum urine and laboratory data can assist in evaluation. For example, in anion gap acidoses caused by toxins such as ethanol, methanol, and ethylene glycol, the toxins (and their metabolites) accumulate in the serum and contribute to the measured osmolality. However, the estimated osmolality, derived from the serum electrolytes, blood urea nitrogen, and glucose, "misses" the new osmols, and an osmolar gap (OG) can be detected by subtracting the estimated osmolality from the actual measured osmolality.

$$OG = \text{Measured osmolality} - 2 \times (Na + K) + BUN/2.8 + Glucose/18 \quad \text{(Equation 5)}$$

An osmolar gap > 10 suggests that one of the preceding toxins (or another unidentified osmotically active substance, e.g., toluene, diethylene glycol) may be present.

Additionally, the *urine* anion gap (urine sodium plus potassium, minus urine chloride) can estimate urinary ammonia excretion. In metabolic acidosis with normal renal acid excretion, unmeasured NH_4^+ usually generates a *negative* urine anion gap. In patients with decreased ammonia excretion, however, the urine anion gap is positive. This differentiates a normal renal response to a gastrointestinal loss of bicarbonate from a renal tubular acidosis in which there would likely be a positive urine anion gap (because of decreased ammonia excretion in RTAs). In ketoacidosis or ethylene glycol ingestion, the unmeasured anions appear in the urine, generating a positive urine anion gap as well.

Management

METABOLIC ACIDOSIS

In general, the treatment for all acid-base disorders is to determine and correct the primary cause. Thereafter, therapy for severe acute acidosis is aimed at increasing the pH to greater than 7.2 and the serum $[HCO_3^-]$ to greater than 10 mEq/L. Because the volume of distribution of HCO_3^- varies inversely with the current plasma $[HCO_3^-]$, the dose of HCO_3^- in mEq to be administered can be calculated:

Dose of HCO_3^- in mEq to increase serum bicarbonate to 10 mEq/L =

$$\{0.4 + 2.4/[HCO_3^-]\} \times \text{wt (kg)} \times \{10 - [HCO_3^-]\} \quad \text{(Equation 6)}$$

However, Equation 6 does not account for *continued* production of acid—only the existing deficit. Thus, monitor the effects of therapy closely. The large sodium load associated with $NaHCO_3$ administration may be limiting, especially in states of volume overload, and consider hemodialysis if medical therapy is not successful immediately. Also consider the risks as well as the possible benefits of $NaHCO_3$ treatment. For example, bicarbonate treatment can acutely raise serum pH and cause hypokalemia and hypocalcemia. Rebound alkalosis will occur if excessive HCO_3^- is given to patients with ketoacidoses and lactic acidosis, as these organic anions will be recycled back to bicarbonate ions during recovery from the inciting event. Alkalemia increases the production rate of many organic acids, including lactic acid, ketoacids, formic acid, and oxalic acid. Alkalemia also increases hemoglobin's affinity for O_2, reducing oxygen delivery to tissues (Appendix A). As HCO_3^- is administered, it is titrated by non-HCO_3^- buffers, increasing $Paco_2$ and the demand for ventilation. Also, the rise in $Paco_2$ may depress central nervous system function, because CO_2 (but not HCO_3^-) enters the cerebrospinal fluid rapidly and decreases cerebrospinal fluid pH.

In studies of patients with acute mild to moderate metabolic acidosis, HCO_3^- therapy has not been shown to improve patient outcome. HCO_3^- therapy is not beneficial during cardiac resuscitation and may be harmful. Thus, the role of HCO_3^- therapy in acutely ill patients is controversial and continues to deserve further study.

Although the treatment of methanol and ethylene glycol intoxication follows the preceding paradigm, it is also essential to decrease the metabolism of these toxins (Chapter 57). Avoid

alkalemia because it accelerates metabolism of methanol and ethylene glycol. Hemodialysis removes these toxins effectively. In salicylate toxicity, aggressively use sodium bicarbonate to promote alkalemia and an alkaline urine, to prevent tissue deposition of the undissociated form of the salicylic acid and to enhance its renal excretion. However, hemodialysis also effectively removes salicylate and should be considered if renal failure is present or the ability to give sodium bicarbonate is somehow limited—for example, if there is preexisting volume overload. Consider hemodialysis if salicylate levels exceed 80 mg/dL, irrespective of the presence of renal failure or other metabolic abnormalities.

Correcting chronic hyperkalemia increases renal ammoniagenesis that, in turn, will increase net H^+ excretion. Strategies for this correction include increasing NaCl intake with or without a diuretic, providing a K^+-removing resin like sodium polystyrene sulfonate (Kayexalate), or administering the synthetic mineralocorticoid fludrocortisone acetate. Diuretic use alone can be counterproductive when Na intake is limited, because the consequent reduction in extracellular fluid volume reduces urine flow in the distal nephron, limiting net H^+ and potassium excretion.

METABOLIC ALKALOSIS

In most cases of alkalosis, the cause (e.g., vomiting or diuretics) is obvious. When extracellular volume depletion exists, treatment centers on repleting volume as NaCl and, if necessary, as KCl. If the cause is less obvious, urine chloride measurements can help one to decide whether repleting volume will be beneficial. In cases of mineralocorticoid excess, treatment with K^+-sparing diuretics such as spironolactone (an aldosterone receptor blocker) or amiloride or triamterene (to directly block Na^+ reabsorption) is useful. In cases of suspected diuretic and laxative abuse, urine chloride values can be misleading and drug screens are helpful.

In patients on ventilators, correcting metabolic alkalosis by repleting potassium and volume deficits can assist weaning. Treatment with carbonic anhydrase inhibitors may also help, although K^+ losses may increase, and the inhibitor's ability to induce bicarbonaturia is blunted by volume depletion. Correction of potassium deficits in patients with liver disease reduces renal ammoniagenesis and may ameliorate hepatic encephalopathy.

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CHAPTER 84

Disorders of Water Homeostasis: Hyponatremia and Hypernatremia

Siddharth P. Shah ■ Joel D. Glickman

Dysnatremias are common in the intensive care unit (ICU) and associated with increased morbidity and mortality. Among patients with *hypernatremia*, the very young and the very old are at particular risk. Published mortality rates range between 16% and 43% in critically ill adults. Similarly, *hyponatremia* increases the mortality rate approximately threefold and increases the likelihood of requiring intensive care and mechanical ventilation within 48 hours of admission, mean length of stay, and hospital costs.

Principles of Body Water

Disorders of sodium *concentration* are a result of changes in *water* balance, not changes in *sodium* balance. Abnormalities in sodium balance typically manifest as a fluctuation in volume status, though rarely they can also present with signs and symptoms of abnormal water balance.

Total body water (TBW) varies mainly with body weight, but it is also a function of age, sex, and fat content. It is difficult to determine the actual TBW in an ICU patient. TBW is generally assumed to be 50% to 60% of body weight in the idealized patient (50% × body weight for women and 60% × body weight for men). However, TBW may be a considerably lower percentage of body weight in the morbidly obese, and conversely as high as 70% to 80% TBW in patients with anasarca and ascites. Hence, clinical judgment and caution are essential in applying recommendations such as the algorithms in Figures 84.E1 and 84.E2 to individual ICU patients.

The distribution of TBW into the intracellular fluid compartment (ICF) and extracellular fluid compartment (ECF) is determined by the osmotically active particles (osmoles) in each compartment. The ECF is composed of the intravascular and interstitial spaces. These compartments and spaces exist in osmotic equilibrium with each other, and water moves between compartments to maintain iso-osmolality. Either water moving between compartments or a change in TBW can alter the serum sodium concentration.

Water movement changes the distribution of TBW from one space to another. For example, when an osmole such as glucose is rapidly added to the ECF, water moves from the ICF to the ECF to maintain iso-osmolality between the cells and ECF, and ECF enlarges while the ICF shrinks. However, maintenance of cell volume is paramount to maintaining cell function. The cell can create additional intracellular osmoles ("idiogenic" osmoles) to prevent water movement from the cell to the ECF and thereby minimize cell shrinkage. Similarly, adding water to the ECF decreases the ECF osmolality, driving an influx of water into the cell. As an adaptive response, the cell can then expel solutes to the ECF to mitigate the gain in cell water and corresponding cell swelling.

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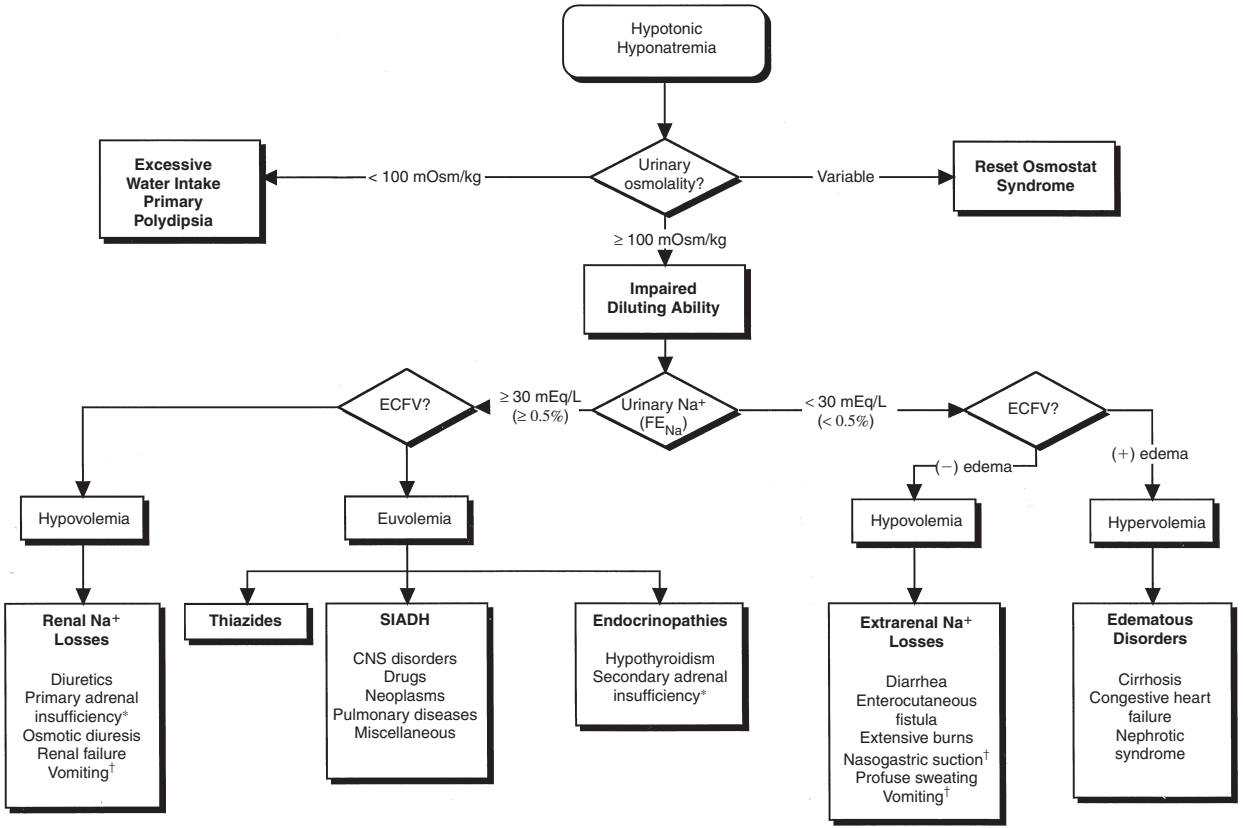


Figure 84.E1 Schematic flow diagram to evaluate hypotonic hyponatremia in ICU patients. Because the normal kidney has an enormous capacity to excrete water, impaired renal diluting ability is the underlying cause of most hyponatremia. ECFV, extracellular fluid volume; FE_{Na}, fractional excretion of sodium = $100 \times (U_{Na} \times S_{Cr})/(S_{Na} \times U_{Cr})$, where S_{Na} is the serum sodium concentration, U_{Na} is the urine sodium concentration, and S_{Cr} and U_{Cr} are the serum and urine creatinine concentrations, respectively. The cutoff value for urine sodium concentration (30 mEq/L) is derived from hyponatremic patients proved to be either hypovolemic or euvolemic by their response to intravenous isotonic saline.

**Cortisol deficiency is associated with elevated plasma vasopressin levels, accounting for the euvolemic hyponatremia characteristic of secondary adrenal insufficiency; in patients with primary adrenal insufficiency (with glucocorticoid and mineralocorticoid deficiency), however, lack of aldosterone leads to renal sodium wasting and extracellular volume contraction.*

†Vomiting and nasogastric suction are associated with sodium chloride depletion and metabolic alkalosis. In steady-state metabolic alkalosis, U_{Na} is low, reflecting hypovolemia; during episodes of vomiting (or intermittent nasogastric suction), however, acute elevations in the serum bicarbonate concentration lead to bicarbonaturia and obligate urinary cation (sodium and potassium) loss.

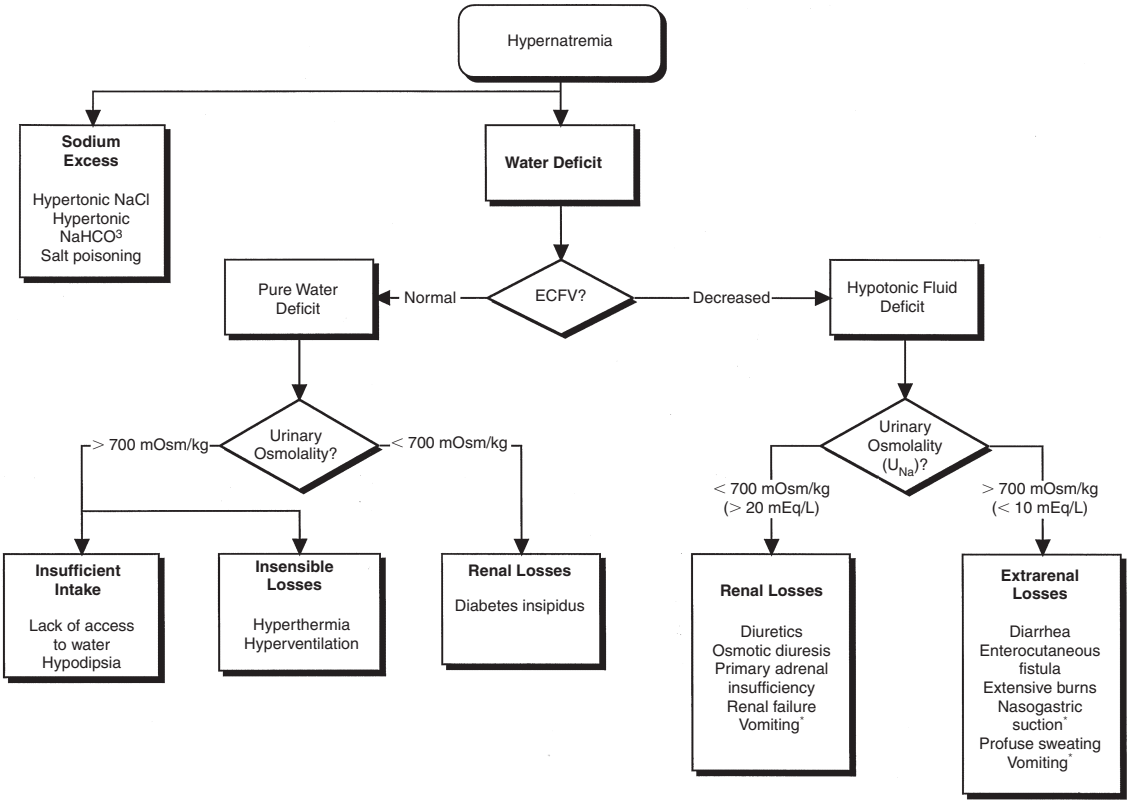


Figure 84.E2 Schematic flow diagram to evaluate hypernatremia in ICU patients. Because hypernatremia is a potent stimulus to thirst, sustained hypernatremia always implies inadequate water intake. The cutoff value for renal concentrating ability (700 mmol/kg) is derived from hospitalized patients with no evidence of neurohypophyseal or renal disease. Precise cutoff values for the urine sodium concentration in hypernatremic patients with renal or extrarenal hypotonic fluid losses are not available; those provided should be considered approximations. ECFV, extracellular fluid volume; U_{Na}, urine sodium concentration.

**Vomiting and nasogastric suction are associated with sodium chloride depletion and metabolic alkalosis. In steady-state metabolic alkalosis, U_{Na} is low, reflecting hypovolemia; during episodes of vomiting (or intermittent nasogastric suction), however, acute elevations in the serum bicarbonate concentration lead to bicarbonaturia and obligate urinary cation (sodium and potassium) loss.*

Though the term *osmolality* (molecular particles or osmoles per unit volume) is typically used in discussions of water homeostasis, tonicity or *effective osmolality* (osmotically active particles per volume) is a more appropriate term. For example, if extracellular osmolality is increased by a substance that diffuses into the cell (e.g., blood urea nitrogen [BUN]), there will quickly be no net osmolar concentration gradient between ECF and ICF and no net movement of water. However, if particles are restricted to the ECF, these osmoles are "effective" (tonicity is increased; e.g., glucose), and water will move to equalize osmolality between ECF and ICF.

The kidney adjusts TBW through highly refined mechanisms of urine concentration and dilution that depend on the glomerular filtration rate (GFR), proximal nephron fluid reabsorption, the integrity of the ascending limb of Henle's loop and distal convoluted tubule, the corticopapillary osmotic gradient, and antidiuretic hormone (ADH) and the ability of the collecting tubule to respond to ADH.

The Physiologic Response to a Change in Total Body Water

Hyponatremia

DEFINITION, PRESENTATION, AND CLINICAL MANIFESTATIONS

Hyponatremia, defined as a serum sodium concentration below 135 mEq/L, reflects a relative excess of water in relation to serum (ECF) sodium. In an attempt to maintain osmotic equilibrium, a net movement of water from the ECF to the ICF results in intracellular volume expansion. Changes in cell water content are of greatest consequence in the brain, where increased cell and tissue volume meet the rigid calvarium and elevated intracranial pressure ensues, risking cerebral herniation. Increased cellular water content can also impair normal intracellular metabolic processes.

Neurologic symptoms usually do not occur until the serum sodium concentration falls below 125 mEq/L, when patients typically complain of anorexia, nausea, or generalized malaise. These symptoms can progress to headache, lethargy, confusion, agitation, and obtundation. If cerebral edema is severe, seizures, coma, respiratory arrest, and death can occur. The morbidity and mortality associated with hyponatremia are influenced by the magnitude and rate of development of the hyponatremia, the age and gender of the patient, and the nature and severity of underlying diseases. At particular risk are the very young and very old, premenopausal women, patients with pneumonia, patients with heart failure, cirrhotics, and chronic alcoholics.

Symptoms generally resolve with correction of the hyponatremia unless moderate to severe hyponatremia has developed in less than 24 hours. In that case, hyponatremia can be associated with residual neurologic deficits and a mortality rate as high as 50%. In contrast, when hyponatremia develops more gradually, symptoms are less frequent and less severe, such that some patients with profound chronic hyponatremia may remain completely asymptomatic.

WORKUP OF HYPONATREMIA

A pathophysiologic approach to categorize hyponatremias and identify their cause follows a series of questions (see Figure 84.E1):

1. Does the Patient Have Hypotonic Hyponatremia?

Hypotonic hyponatremia (sometimes referred to as *true* hyponatremia) is associated with plasma hypo-osmolality and relative TBW excess. This is distinct from *isotonic* hyponatremia and *hypertonic* hyponatremia, which are not hypo-osmolal states.

When the body is in water balance, the serum sodium concentration is stable and water outputs are being matched by water input. Osmoreceptors in the hypothalamus monitor the plasma osmolality (largely determined by the serum sodium concentration) and maintain osmolality or attempt to correct it through control of thirst and ADH output.

Response to free water addition: When water is added to the body, the fall in plasma osmolality (or development of even mild hyponatremia) should abolish thirst and suppress ADH secretion. In the absence of ADH, the kidney eliminates the excess water by producing dilute urine (approximately 50 to 100 mOsm/kg). A healthy kidney can excrete up to 20 liters of "free" water (the equivalent of solute free water) per day, which exceeds the amount of water most people consume. Hyponatremia (a net increase in TBW) occurs when the kidneys' ability to excrete water is impaired or exceeded.

Response to free water loss: A healthy individual experiences obligatory daily water losses (outputs) in the stool and urine. Also, evaporative losses occur from the skin and respiratory tract, equal to ~500 mL/day. This evaporative loss is minimal when the patient is mechanically ventilated, because the ventilator delivers an inspiratory air mixture that is heated and close to fully humidified. These losses must be balanced by water intake to maintain water homeostasis and a stable serum sodium concentration. If the body loses water and it is not replaced, plasma osmolality rises (and hypernatremia develops). This stimulates thirst and increases ADH secretion. ADH minimizes renal water elimination, resulting in concentrated urine (~1000 to 1200 mOsm/kg). Although this can diminish water loss from the kidney, the original water deficit cannot be corrected without supplementing oral or intravenous water.

To fully comprehend the pathophysiology of abnormal water status, one must account for both (1) net water gain or loss and (2) the renal response to the abnormality in water status. As noted in the preceding example, when hypernatremia occurs from water loss, even a completely normal kidney cannot restore serum sodium to normal unless more water is added. An abnormal renal response may exacerbate the hypernatremia. Similarly, although hyponatremia occurs from a net addition of water to the body, hypo-osmolality is often sustained by insufficient renal water excretion.

Quantifying urinary free water excretion can help answer three key questions: (1) How did the patient develop this dysnatremia? (2) Will the patient self-correct the disorder? and (3) How fast will changes in water content occur? Quantification of water excretion identifies how the kidneys are handling water during a specific time frame. This relies on the theoretic separation of the urine into an isotonic compartment (relative to the serum) and a water (i.e., solute-free) compartment. The quantity of water in this model may be a negative or positive number, representing the net addition to or subtraction from TBW, respectively. This theoretic quantity, the urinary *electrolyte-free and solute-free* water clearance, offers the optimal way to both conceptualize and quantify urine *water*.

In *hypertonic hyponatremia*, large amounts of solutes restricted to the ECF (such as glucose and mannitol) result in water movement out of the cells. The redistribution of water to the ECF thereby reduces the sodium concentration, as commonly seen in severe hyperglycemia. For every 100-mg/dL increase in the serum glucose concentration above 400 mg/dL, one can expect a 2.4-mEq/L reduction in the serum sodium concentration. (Or alternatively, as stated in Chapter 82, every 100 mg/dL of glucose greater than 100 mg/dL decreases the serum sodium by ~1.6 mEq/L.) Two common scenarios where this is seen are (1) uncontrolled diabetes (see Chapter 82) and (2) iatrogenic delivery of a high solute load (e.g., intravenous immune globulin [IVIG] is commonly delivered in a fluid with high sugar content). In this case, unlike hypotonic hyponatremia, cells are *dehydrated*. Treatment focuses on correcting the underlying cause of increased serum osmolality (e.g., insulin).

Theoretically, true isotonic hyponatremia occurs if an isotonic solution without sodium is added to the ECF (e.g., glycine irrigation solution). The solutes in such a solution must be restricted to the ECF for hyponatremia to be sustained. In the past, *isotonic hyponatremia* was considered pseudohyponatremia, a laboratory artifact, in the setting of hyperlipidemia or paraproteinemia. Newer laboratory techniques directly measure serum sodium and avoid this error. The distinction between hypotonic, isotonic, and hypertonic hyponatremia can be made by measuring the serum osmolality.

2. In Hypotonic Hyponatremia, Are Renal Diluting Mechanisms Functioning at Capacity?

The normal response to water ingestion producing even slight hyponatremia is the excretion of dilute urine (urine osmolality < 100 mOsm/kg). Hence, a urine osmolality less than 100 mOsm/kg points to an appropriate renal response to hyponatremia, as seen clinically with excess water intake (e.g., polydipsia) or a low solute diet (e.g., beer potomania). When the urine osmolality exceeds 100 mOsm/kg during hyponatremia, an impairment of renal diluting ability limits water excretion by the kidney.

3. Why Is Renal Diluting Ability Impaired (as Evidenced by an Inappropriately Elevated Urine Osmolality)?

Impaired urine dilution (urine osmolality > 100 mOsm/kg) may result from (1) decreased delivery of fluid to the renal diluting segment (decrease in GFR or increased proximal tubular reabsorption of glomerular filtrate as a result of volume contraction), (2) abnormalities in dilution of the filtrate in the diluting segment (ascending limb of the loop of Henle and early distal convoluted tubule), or (3) persistently elevated vasopressin (ADH) activity. Of these mechanisms, increased ADH activity (from increased ADH levels or increased sensitivity to ADH) is the most important and most common underlying pathophysiology in ICU patients. Elevated ADH activity often results from low effective arterial blood volume (EABV), as seen in states of whole body hypovolemia or whole body volume excess (e.g., cirrhosis, congestive heart failure, or nephrosis).

Normally, hypo-osmolality potently inhibits ADH release. However, the homeostatic defense against volume contraction supersedes the regulation of serum osmolality: to maintain intravascular volume, the body retains water accepting lowering tonicity. With low EABV, carotid baroreceptors initiate a neural pathway triggering *nonosmotic* ADH release. ADH increases the collecting duct permeability to water, which facilitates water reabsorption. If the alert patient drinks excessive water through nonosmotic stimulation of thirst (from hypovolemia), or the patient ingests even a "normal" or subnormal amount of water, hyponatremia can progress further. Causes of low EABV are divided into whole body *hypovolemic states* and *hypervolemic states*.

Hypovolemia can result from renal or extrarenal volume losses. The patient may exhibit overt signs of volume depletion such as tachycardia, orthostatic hypotension, and organ hypoperfusion. Laboratory indices such as an elevated BUN to creatinine ratio (BUN:creatinine > 20) or an elevated serum uric acid level may help identify subclinical volume loss in ICU patients. With extrarenal volume loss, the urine sodium is typically below 20 mmol/kg. Common causes for *extrarenal*

A serum sample contains both aqueous and nonaqueous components. The *actual* sodium concentration is based on the amount of sodium and water in the aqueous component. However, with one method of measuring sodium, the *reported* sodium concentration is based on the amount of sodium per volume of total serum (aqueous and nonaqueous). Therefore, if the nonaqueous part of the serum is increased from marked hypertriglyceridemia or paraproteinemia, the aqueous component of the serum is decreased and the total amount of sodium in that total serum sample volume is decreased.

volume loss include vomiting, diarrhea, bleeding, and "third-spacing" of fluids (e.g., pancreatitis, trauma, sepsis-induced increased vascular permeability).

Renal volume loss occurs from diuretic use, hypoaldosteronism, metabolic alkalosis, sodium-wasting nephropathies, or cerebral salt wasting. In each of these causes, urine sodium typically exceeds 20 mmol/kg. *Cerebral salt wasting* (CSW) has emerged as an important clinical entity in neurosurgical patients with intracranial pathology. This diagnosis is made based on evidence of defective renal sodium transport, inappropriate urinary salt wasting, and decreased EABV (negative sodium balance). This volume contraction distinguishes CSW from the syndrome of inappropriate antidiuretic hormone (SIADH), which usually represents a slightly volume-expanded state.

The administration of intravenous fluids to patients with intracranial disease can make the volume status and renal sodium excretion difficult to interpret. However, demonstration of inappropriately negative salt balance argues for CSW. One theoretic mechanism for CSW suggests that CNS injury disrupts the autonomic nervous system stimulation of basal proximal tubular sodium and urate reabsorption. Another theory posits that injured CNS cells elaborate brain natriuretic peptide (BNP), which inhibits renal sodium reabsorption. Elevated BNP levels have been demonstrated in patients with subarachnoid hemorrhage. Details regarding the diagnosis and pathophysiology of CSW remain controversial. Clinically, distinguishing CSW from SIADH is important because the management differs dramatically. CSW treatment focuses on correcting hypovolemia, whereas SIADH treatment includes water restriction, increasing free water excretion, and correcting the renal diluting defect.

Low EABV can also occur in conditions where the patient is whole body volume overloaded. Congestive heart failure (CHF), cirrhosis, and nephrotic syndrome each typify this scenario. Excess fluid accumulates in the interstitial spaces ("third spacing") and peritoneal cavity; the EABV, necessary to establish a mean arterial pressure and perfuse organs, remains relatively low. This can result from a poor cardiac output (CHF), vascular dilation and blood volume redistribution into systemic arteriovenous fistulae (cirrhosis), or low oncotic pressure from hypoalbuminemia (nephrotic syndrome). In each of these processes, the decrease in EABV leads to (1) nonosmotic stimulation of ADH release, (2) decreased GFR and decreased delivery of fluid to the distal nephron, and (3) potential nonosmotic stimulation of thirst.

4. If EABV Is Adequate, What Is Causing the Nonosmotic and Nonhemodynamic Stimulation of ADH Release?

Many patients with true hyponatremia do not have overt signs of hyper- or hypovolemia: water excess exists without a clinically significant volume abnormality. This results from abnormal renal water excretion (typically mediated by ADH) from several possible causes: (1) use of ADH analogues (e.g., desmopressin [DDAVP] or oxytocin), (2) use of drugs that potentiate ADH release or action (see Box 84.1), (3) presence of adrenal insufficiency, (4) presence of hypothyroidism, (5) SIADH, and (6) a "reset osmostat" syndrome.

SIADH is the most common etiology of hyponatremia in hospitalized patients (Box 84.1), encompassing conditions of elevated circulating ADH levels (from enhanced hypothalamic secretion or ectopic production) or potentiated effects of normal ADH levels. The diagnosis is made when hypotonic hyponatremia coincides with an inappropriately concentrated urine (urine osmolality > 100 mOsm/kg) and other medical conditions are excluded. Plasma vasopressin levels do not differentiate SIADH from other causes of hyponatremia.

The reset osmostat syndrome accounts for as many as one third of cases that at first sight appear to be classic SIADH. A formal water load can distinguish the two conditions but is dangerous to perform in severely hyponatremic patients. Unlike SIADH, patients with a reset osmostat defend body fluid tonicity around a depressed osmolality set point and usually have only mild

Box 84.1 Causes of Syndrome of Inappropriate Diuretic Hormone (SIADH)

CNS Disease

Brain tumor: primary or metastatic, infections: abscess, encephalitis, meningitis (including tuberculous meningitis), Guillain-Barre syndrome, subarachnoid hemorrhage, subdural hematoma, acute intermittent porphyria, hypothalamic sarcoidosis, pituitary surgery, skull fracture, traumatic brain injury

Tumors

Small cell lung cancer, Hodgkin's disease, duodenal adenocarcinoma, pancreatic adenocarcinoma, lymphosarcoma, thymoma, bladder, prostate, and uterine cancers

Lung Disease

Pneumonia, empyema, lung abscess, atelectasis, pneumothorax, lung cancers, tuberculosis

Medications

Cyclophosphamide and ifosfamide; vincristine and other vinca alkaloids; antipsychotics: thiothixene, haloperidol, thioridazine, fluphenazine; antidepressants: amitriptyline, monoamine oxidase inhibitors, fluoxetine, sertraline; nonsteroidal anti-inflammatory agents (NSAIDS), clofibrate, chlorpropamide, carbamazepine, methamphetamines, oxytocin, opioids

Miscellaneous

Pain, surgical and medical stress, severe nausea, positive-pressure ventilation, idiopathic, AIDS

hyponatremia. Because their hyponatremia does not decrease below the depressed set point, water restriction is not required.

TREATMENT OF HYPONATREMIA

Overt neurologic symptoms usually begin to occur when the serum sodium concentration falls to less than 125 mEq/L; however, subtle cognitive abnormalities can exist with milder hyponatremia. Symptoms reflect varying degrees of cerebral edema and brain cell dysfunction, and the differing management of hypertonic and isotonic hyponatremia is discussed below. In hypotonic hyponatremia, the principal aims of treatment are to increase the serum tonicity above the neurologic "danger range" and to correct the underlying cause of hyponatremia. The magnitude and rate of correction of the serum sodium account for how cells have adapted to their hypotonic environment over time. In *chronic* hyponatremia, brain cells adapt to the hypotonic ECF by reducing their intracellular solute content. Cells extrude electrolytes to the ECF during the first 6 to 12 hours of adaptation. Over the next 24 to 72 hours, organic solutes (largely amino acids) are lost more slowly or are osmotically inactivated. Thus, full adaptation may take several days. Over-rapidly correcting or simply overcorrecting the tonicity of a patient with *chronic* hyponatremia risks osmotically induced CNS demyelinization (discussed later).

Asymptomatic Hyponatremia

The majority of patients with mild to moderate hyponatremia (serum sodium concentration between 120 and 135 mEq/L) are relatively asymptomatic. The ideal treatment of hyponatremia from stimulation of ADH release by a low EABV is to restore effective circulating volume. In *hypovolemic* patients, treatment is directed at correcting volume depletion, with isotonic (0.9%) saline if intravenous therapy is indicated to stabilize the blood pressure. Volume repletion readily elicits a water diuresis by delivering fluid to the renal diluting segment and suppressing ADH release; this can cause a dramatic increase in water excretion and correction of hyponatremia. The clinician should identify and correct the cause of the excessive volume loss.

Resolution of hyponatremia associated with any of the edematous disorders ultimately depends on correction of the process responsible for the low EABV. At times this may not be possible, so the mainstay of therapy for the hyponatremic edematous patient remains water restriction. Diuretics are often a double-edged sword. They may be needed to treat pulmonary vascular congestion, peripheral edema, and ascites, but excessive use can worsen effective arterial hypovolemia and exacerbate water retention. Strategies directed at increasing EABV, such as inotropes and afterload reduction, can ameliorate hyponatremia in patients with CHF (Chapter 52).

In patients with hyponatremia and an adequate EABV (euvolemic hypotonic hyponatremia), treatment is targeted to (1) eliminate the cause for persistent ADH activity and (2) restrict water intake to match daily water losses (stool, urine, evaporative). In SIADH, discontinue offending medications and identify treatable causes. Water reabsorption from the collecting duct occurs as a result of an osmotic gradient between the intraluminal fluid (in the collecting duct) and the surrounding hypertonic renal interstitium. The increased tonicity of the interstitium near the loop of Henle, generated by sodium and chloride reabsorption without water, can be blocked with loop diuretics. In this way, furosemide can diminish the interstitial tonicity and therefore diminish the gradient that would normally cause water reabsorption. The resultant volume contraction (a side effect of this therapy) can be ameliorated by the co-administration of sodium chloride tablets. Additionally, the solute content provided by NaCl tablets facilitates water excretion by the kidney. If these therapies are insufficient to maintain the serum sodium concentration above 130 mEq/L, adjunctive therapy with *demeclocycline* may be of benefit. This agent blocks vasopressin-mediated water reabsorption in the collecting duct.

Finally, a newer class of agents known as nonpeptide vasopressin receptor antagonists, or *vaptans*, has been developed. These agents increase electrolyte-free water excretion and thereby increase the serum sodium concentration. Water restriction must be maintained, as these agents stimulate thirst. However, despite the improved serum sodium concentration with the administration of these agents, the majority of outcomes trials have failed to show a clinical benefit. Two agents, conivaptan and tolvaptan, have been approved for use in the United States for patients with hyponatremia from CHF. Clinical experience with the use of these agents is limited, especially in critically ill patients.

Symptomatic Hyponatremia

Severe hyponatremia can be life threatening, and usually requires immediate therapy. This scenario is uncommon when the serum sodium concentration is > 120 mEq/L. Irrespective of cause, the objective of therapy is the same: to raise body fluid tonicity and shift water out of the intracellular space, thereby ameliorating cerebral edema. The rate of correction must be carefully regulated. Overly rapid correction has been associated with *central pontine myelinolysis,* or when extrapontine, *osmotic demyelinization syndrome*. This process is characterized by the destruction of the myelin sheath surrounding nerve cells in the brain stem. Osmotic demyelinization typically occurs 2 to 6 days after the initiation of treatment and manifests as dysarthria, dysphagia, incoordination, quadriplegia, and, in severe cases, coma. Rapid correction is particularly risky in patients with *chronic* hyponatremia in whom cell volume adaptations are complete. Osmotic demyelinization occurs most commonly during the treatment of chronic hyponatremia, following the rapid correction of hyponatremia, and especially if hyponatremia is *over*corrected. If correction occurs too rapidly, there is some evidence that reintroduction of mild hyponatremia can decrease the likelihood of neurologic complications. When the duration of hyponatremia is unknown or the magnitude of hyponatremia is severe, correction should proceed at a cautious pace in conjunction with a nephrology consultant.

As a general rule, in most cases the serum sodium concentration should increase by no more than 10 mEq/L in the first 24 hours, and by no more than 18 mEq/L in the first 48 hours (i.e., at a rate of approximately 0.5 mEq/L per hour). However, in grave situations (e.g., serum sodium

concentration < 105 mEq/L), initial therapy can be more aggressive—targeting a change in the serum sodium concentration of 1 to 2 mEq/L per hour *for the first few hours only*. The recommended daily target should not be exceeded, with the serum sodium concentration and clinical condition of the patient monitored closely. Full correction should take place over several days, with assiduous avoidance of hypernatremia.

Treatment is best accomplished with 3% hypertonic saline. The amount of sodium administered can be estimated as follows: A 70-kg lean "idealized" man with a serum sodium concentration of 105 mEq/L has a TBW of 35 L (assumed to be equal to 50% of body weight if the patient is not grossly edematous or morbidly obese). The amount of sodium needed to raise his serum sodium concentration by 10 mEq/L is 350 mEq (= 10 mEq/L × 35 L). Hypertonic (3%) saline has a sodium concentration of 513 mEq/L (= 154 mEq [in 0.9% saline] × 3/0.9); therefore, about 680 mL of 3% saline (350/513 × 1000 mL) would be required in the first 24 hours. If these calculations are not readily available and the patient's condition is emergent, another temporizing option is to give 100 mL of 3% saline (51 meq) rapidly. This will quickly raise serum sodium by slightly less than 2 meq/L and provide the clinician with the opportunity to develop a more comprehensive diagnosis and treatment plan. Because they take no account of ongoing sodium and water losses, these calculations provide only a rough estimate. Frequent measurements of the serum sodium concentration (initially every 2 hours) are mandatory to adjust the rate of correction. One should also be aware that rapid extracellular volume expansion with hypertonic saline can precipitate pulmonary edema, especially in patients with underlying heart disease. If this is a consideration, a loop diuretic (furosemide) can be administered simultaneously with the 3% saline.

Isotonic saline alone should never be used to treat hyponatremia in *euvolemic* patients with SIADH, since water retention and salt excretion may actually worsen hyponatremia. The use of isotonic saline and furosemide in SIADH is also not recommended. Although effective, the rise in the serum sodium concentration is less predictable than with 3% saline, and large urinary potassium and magnesium losses often complicate the clinical picture.

Hypernatremia

DEFINITION, PRESENTATION, AND CLINICAL MANIFESTATIONS

Hypernatremia is defined as a serum sodium concentration in excess of 145 mEq/L. It typically results from inadequate water intake, excessive loss of water without replacement, or, extremely rarely, a true sudden and dramatic intake of sodium. In hypernatremia, a relative deficit of water to sodium in the ECF causes water to move out of cells to restore osmotic equilibrium. The resultant loss of cell volume, particularly in the brain, causes the observed central nervous system (CNS) symptoms. CNS symptoms range from agitation, restlessness, confusion, and lethargy to stupor and coma. Other signs and symptoms include nausea, vomiting, muscle weakness, fasciculations, and seizures. Reduction in brain volume in patients with hypernatremia may predispose them to intracerebral, subarachnoid, or subdural hemorrhage.

The presentation of hypernatremia depends on both the magnitude and the rate of rise of the serum sodium concentration. In general, a higher serum sodium concentration more greatly depresses the sensorium, and acute changes are tolerated more poorly than chronic changes. Overt symptoms are unusual until the serum sodium concentration rises to greater than 150 to 155 mEq/L. They typically resolve with correction of hypernatremia. Permanent neurologic deficits may occur, particularly when acute severe hypernatremia overwhelms the brain's volume regulatory defenses. When hypernatremia develops more gradually, symptoms are both less frequent and less severe. Some patients with chronic hypernatremia may be completely asymptomatic.

Changes in ECF volume and the presence of comorbid conditions commonly modify the presentation of hypernatremia—they may even dominate the clinical picture. For example, hypernatremia secondary to excess salt is frequently associated with symptoms of volume overload, whereas hypernatremia that results from the loss of hypotonic fluids is associated with signs of extracellular volume depletion. The magnitude of changes in extracellular fluid volume may require treatment precedence over the hypernatremia.

WORKUP OF HYPERNATREMIA

Hypernatremic disorders can be broadly organized according to the clinical volume status of the patient—hypovolemic (common), euvolemic (common), and hypervolemic (rare) (see Figure 84.2). Individual disorders within each of the broad volume categories will highlight where normal physiology has gone awry. Recall that the sum of the body's defenses against hypernatremia are (1) thirst and water intake and (2) renal conservation of water.

Hypovolemic Hypernatremia

Hypovolemia is common in critically ill patients because of the number of processes that lead to both sodium and water loss. Fluid losses are often hypotonic, causing relatively more water than sodium loss, leading to volume contraction and hypernatremia. The healthy kidney attempts to retain filtered water in the distal nephron. Evidence for hypovolemia can include signs of end-organ hypoperfusion, tachycardia, orthostatic hypotension, and poor skin turgor.

Loss of hypotonic fluid can be from renal or extrarenal sources. These can be distinguished by measuring the urine sodium, which is > 20 mmol/L in renal loss and < 20 mmol/L in extrarenal loss. Renal losses may result from an osmotic diuresis, postobstruction diuresis, loop diuretic use, and intrinsic renal disease impairing the kidney's concentrating ability. Extrarenal losses include dermal loss from excessive sweating and burns, osmotic diarrhea (lactulose, malabsorption, postsurgical diverting stoma with high output, and specific infectious diarrheas), fistulae, open body cavities (postsurgical), and draining fluid accumulations with hypotonic output. Treatment (discussed in detail below) consists of correcting both the volume deficit and the water deficit, as well as treating the underlying disorder.

Euvolemic Hypernatremia

Patients with "euvolemic" hypernatremia have a loss of TBW without *clinically significant* volume loss. The variable urine sodium concentration does not discern among the diagnostic possibilities.

As before, water loss can be of renal origin or extrarenal origin. Healthy individuals consume enough water to compensate for typical insensible (or sometimes sensible) extrarenal water loss from the skin and lungs. Insufficient water intake may result from impaired thirst (hypodipsia) or access to adequate amounts of water (obtunded or bedridden). Many elderly individuals have impaired thirst, and when dehydrated, sense less thirst and drink less than younger individuals, putting them at increased risk for hypernatremia. In febrile and hypermetabolic states, evaporative (sensible and insensible) losses may increase beyond the ability of the individual to consume water. Even when the renal ability to concentrate the urine and retain water is fully intact, the prevailing rate of evaporative loss exceeds water intake and the patient becomes progressively hypernatremic. This is rare in otherwise healthy individuals with access to water.

Renal water loss in the setting of hypernatremia/hyperosmolarity identifies a deficit in renal concentrating ability. "Euvolemic" hypernatremia results from (1) insufficient ADH production or release (central diabetes insipidus) or (2) insufficient response to ADH in the collecting tubules (nephrogenic diabetes insipidus). Defective generation or maintenance of the corticopapillary osmotic gradient (protein malnutrition, diuretics, osmotic diuresis, renal failure) may also impair concentrating ability. Osmotic diuresis (see the above discussion of hypovolemic hypernatremia)

can often present without clinical volume contraction, particularly in patients receiving a high osmolar load (e.g., total parenteral nutrition [TPN]) who must eliminate large amounts of urea and large amounts of water with it.

Diabetes insipidus (DI) results in inappropriate renal water wasting (water diuresis), polyuria, and polydipsia (in the alert patient). *Polyuria* is defined as urine output in excess of 3 liters per day. In the absence of DI, polyuria can result from a high osmolar load or solute diuresis (diuretics, salt ingestion, vomiting/bicarbonaturia, mannitol, glucose, TPN). Most non-critically ill patients with DI maintain water balance with only a minor elevation of the serum sodium concentration, from a preserved thirst mechanism and unrestricted access to water. However, ICU patients are often unable to drink water or express thirst, and therefore more severe hypernatremia ensues.

Any hypothalamic pathology may result in ADH insufficiency and central DI (Box 84.E1). No clear cause is identified in more than 50% of patients. At least 80% of the vasopressin-secreting neurons must be destroyed before clinically significant symptoms appear. The diagnosis of DI is usually obvious if the patient presents with hypernatremia and dilute urine (osmolality < 250 to 300 mOsm/kg). Urine output can range from 3 to 20 liters per day. If the diagnosis is unclear, it may be helpful to (1) assess for the *absence* of an appropriate increase in urine osmolality during a water deprivation study (only performed after correction of hypernatremia) and (2) assess for a response to exogenous ADH. In DI, patients fail to concentrate their urine when water is withheld, and the urine osmolality remains low. In central DI, exogenous vasopressin administration decreases urine output and increases urine osmolality. These studies should be performed in conjunction with a renal consultant, as time course and trajectory must be carefully considered when attempting to correct hypernatremia (see "Treatment of Hypernatremia," presented later in the chapter). Subtle forms of DI (i.e., partial DI) can also occur, however these are difficult to diagnose in critically ill ICU patients. DI after head trauma or surgery may be transient, permanent, or even follow a triphasic course. The transient form is most common, with an abrupt onset within the first 24 hours and then resolution within several days or weeks. The permanent form also has an abrupt onset within the first 24 hours but does not resolve. In the triphasic pattern, there is an initial period of vasopressin deficiency lasting 2 to 4 days (resulting from axonal injury), a 5- to 7-day period of inappropriately high vasopressin release (because of leakage from the degenerating neurons) and, finally, permanent central DI once neurohypophyseal stores are depleted.

Nephrogenic DI also has many causes (see Box 84.E2). It can be readily differentiated from central DI by the patient's failure to respond to exogenous vasopressin. Urine volumes are typically less than 4 liters per day because some non-aquaporin–mediated urinary concentrating mechanisms remain functional.

Hypervolemic Hypernatremia

It is uncommon for an increase in total body sodium, rather than a loss of water, to disrupt the ratio of sodium:water to create hypernatremia. However, in the hospital this important cause of iatrogenic hypernatremia typically follows overzealous treatment of *hypo*natremia or metabolic acidosis. The 3% saline solution commonly employed in the treatment of severe *hypo*natremia contains 513 mEq of sodium per liter. Even more hypertonic is the 7.5% sodium bicarbonate solution (44.5 mEq of sodium per 50 mL ampule; or 890 mEq/L of sodium) sometimes used during cardiopulmonary resuscitation. High sodium feedings also represent a potential sodium load. In these situations, the large amount of sodium delivered increases ECF volume and the patient may exhibit signs of volume overload.

TREATMENT OF HYPERNATREMIA

The thrust of treatment in hypernatremia is to correct the serum osmolality by providing much needed water. However, as evidenced by the grouping of these disorders described earlier,

Box 84.E1 Causes of Hypothalamic Diabetes Insipidus

Head trauma

Pituitary surgery

Neoplasia

Pituitary adenoma, craniopharyngioma, dysgerminoma, pinealoma, glioma, metastatic carcinoma (breast, lung), leukemia, lymphoma

Vascular lesions

Ruptured aneurysm, cavernous sinus thrombosis, hypertensive encephalopathy, Sheehan syndrome (postpartum pituitary infarction)

Infections

Encephalitis, meningitis, tuberculosis, syphilis

Granulomatous diseases

Sarcoidosis, histiocytosis X

Miscellaneous

Hypoxic encephalopathy, idiopathic, hereditary forms, pregnancy

Box 84.E2 Causes of Nephrogenic Diabetes Insipidus

Drugs

Lithium, demeclocycline, amphotericin B, methoxyflurane

Electrolyte Disorders

Hypercalcemia, hypokalemia

Renal Disorders

Obstructive nephropathy, postobstructive diuresis, diuretic phase of acute tubular necrosis, renal transplant

Miscellaneous

Sjögren's syndrome, amyloidosis, multiple myeloma, sickle cell anemia, hereditary forms

correcting the volume status is often equally and sometimes more important. Specific treatment recommendations must take into account two concepts. First is quantification of the relative deficit of water. This calculation determines how much water is needed to add to the body to normalize the serum sodium concentration (assuming that total body sodium is constant). Multiplying *normal* TBW (60% of body weight for idealized men and 50% of body weight for idealized women) by the ratio of (normal [Na+]/current [Na+]) gives the *current* TBW. Subtracting *current body water* from *normal body water* gives the *water deficit*.

$$\text{Normal TBW} = 0.5 \times \text{Total body weight}$$

$$\text{Current body water} = (\text{Normal body water}) \times (140\ \text{mEq/L}/\text{Current } [Na^+])$$

$$\text{Water deficit (L)} = \text{Normal body water} - \text{Current body water}$$

To illustrate, in a non-edematous, non–morbidly obese female patient normally weighing 60 kg, who now presents with a serum sodium concentration of 160 mEq/L, *normal* body water would equal 30 L. However, current body water = (0.5 × 60) × (140/160) = 26.25 L. Thus, the water deficit is 3.75 L (30 L – 26.25 L).

The second concept to address in treatment of hypernatremia is that of chronicity and cellular adaptation. Acute hypernatremia is poorly tolerated and should be treated aggressively. However, in chronic hypernatremia brain cells adapt to the hypertonic ECF by increasing intracellular solute content. In the early phase extracellular salts move into the cell. Later (over 24 to 72 hours), organic solutes such as amino acids accumulate. These additional intracellular salts and solutes diminish the osmotic gradient between ICF and ECF and thereby allow the cell to retain more water; they are the defense mechanisms against cellular dehydration. In a patient whose brain has fully adapted, overzealous treatment with supplemental water risks a potentially unsafe amount of water movement into the ICF because of these new intracellular osmoles. The cells will expand more than desired, potentially yielding clinically significant cerebral edema. The rate of new intracellular solute generation in the brain has not been precisely defined. Because the rapid correction of chronic hypernatremia is dangerous, aggressive therapy should *not* be employed when the duration of the hypernatremia cannot be established with reasonable certainty—potential adverse outcomes include seizures, coma, permanent neurologic sequelae, or death. When the duration of hypernatremia is uncertain, it is safest to assume it is chronic. In that setting no more than half the estimated water deficit should be replaced during the first 24 hours, with careful monitoring of the patient's neurologic status and the serum sodium concentration (every 2 hours at the beginning). The remainder of the deficit can then be replaced over the ensuing 48 hours. The oral route is always preferable provided that the patient is alert and there is no risk of pulmonary aspiration. In ICU patients, replacement can often utilize enteral access devices, such as an oral gastric tube or an oral enteral tube. However, if the latter is postpyloric in location (i.e., in the small bowel), some advise limiting boluses of free water to no more than 250 mL. In other cases, 5% dextrose in water should be administered intravenously. In addition to replacing the water deficit, ongoing water losses should be calculated and replaced.

In *hypovolemic hypernatremia*, prompt restoration of adequate tissue perfusion is paramount. Optimal therapy is isotonic (0.9%) sodium chloride solution administered intravenously at a rate sufficient to stabilize the blood pressure. Once intravascular volume status has been addressed, attention can be turned to the treatment of the hypernatremia itself. Treatment of the etiology of water loss should already be under way (insulin, cessation of osmotic diuretics, antidiarrheal agents), according to the recommendations offered earlier and also accounting for ongoing water loss.

In *euvolemic hypernatremia* tissue perfusion is adequate; therefore, the clinician can focus primarily on correcting the water deficit. If hypernatremia originates from extreme evaporative losses or inadequate water intake (usually iatrogenic in sedated ICU patients), then the water deficit can be replaced as described previously, always accounting for chronicity. Treating underlying

disorders will mitigate ongoing water loss. For *DI*, water ingestion in sufficient quantity to maintain water balance and prevent hypernatremia is the mainstay of therapy.

In *central DI*, hormone replacement decreases polyuria and permits maintenance of water balance with a more tolerable level of water intake. Hormone replacement with desmopressin (DDAVP) can be delivered intranasally at a dose of 10 to 40 mcg/day, divided into one to three doses. The onset of action is within 30 minutes, and the duration of action is 12 to 24 hours. Intravenous or subcutaneous administration is useful in patients in the ICU when intranasal delivery is suboptimal. The usual intravenous or subcutaneous dose is about one tenth of the intranasal dose, or 1 to 4 mcg/day, divided into two doses. An oral form is available for maintenance therapy, though variability in gastrointestinal absorption of oral DDAVP makes a direct dose correlation difficult; titration is typically required. Exogenous DDAVP administration produces a nonsuppressible antidiuretic effect for at least 12 hours. During this time, the patient will have a limited ability to eliminate water, thus water intake should be reduced accordingly to avoid hyponatremia. A corollary to this is that the smallest dose of DDAVP should be used to achieve a tolerable (but not zero) urine output.

Nephrogenic DI does not respond to hormone replacement therapy. Offending drugs should be discontinued, electrolyte disorders corrected, and any other underlying disorders addressed. Water loss occurs in the distal nephron in nephrogenic DI. Although it may seem counterintuitive, the combination of a thiazide diuretic and sodium restriction leads to mild volume depletion, which in turn enhances proximal tubular fluid reabsorption and decreases distal fluid delivery (site of water diuresis), ultimately diminishing water loss and urine output. Protein restriction reduces daily obligate solute excretion, thereby attenuating polyuria. Nonsteroidal anti-inflammatory agents block renal prostaglandin synthesis and enhance vasopressin-independent water reabsorption—they have been used in select patients with nephrogenic DI. Amiloride blocks the uptake of lithium by the renal collecting duct and has been used with some success in the early presentation of *lithium-induced* nephrogenic DI.

In *hypervolemic hypernatremia*, there is excess salt. The same equation used earlier to calculate the water deficit can be used here to estimate the amount of water needed to normalize the sodium concentration. However, in this situation there is no absolute water deficit and the water administered to correct tonicity will increase TBW to greater than normal. In time the kidney will excrete both the excess sodium and additional water. This group of hypernatremias typically develops acutely; if so, then the relative water deficit can be replaced quickly. The *rapid* administration of water should continue only until neurologic symptoms improve. As with all hypernatremias in the ICU, the serum sodium concentration should be monitored closely during treatment since frequent adjustments in the rate of water administration may be needed.

Conclusion

Disorders of water homeostasis and the serum sodium concentration are common in the ICU. They can have grave neurologic sequelae if not managed appropriately. A careful understanding of the underlying pathophysiology helps the clinician to restore the serum tonicity toward normal. Awareness of cellular adaptations to chronic hypo- or hyperosmolar states will allow treatment to occur safely.

An annotated bibliography can be found at www.expertconsult.com.

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This review, published in an international peer-reviewed renal journal, compared and contrasted hyponatremia in 2 major conditions: syndrome of inappropriate anti-diuretic hormone (SIADH) and acquired salt wasting (known as cerebral salt wasting [CSW] or renal salt wasting [RSW]).

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Stelfox HT, Ahmed SB, Khandwala F, et al: The epidemiology of intensive care unit-aquired hyponatremia and hypernatremia in medical-surgical intensive care units. Crit Care 13(2):R162, 2002. Epublication.

This retrospective analysis evaluated more than 8000 consecutive admissions to intensive care units (ICUs) in Canada. The incidence of hyponatremia and hypernatremia were established, as were the prevalence of associated comorbidities and patient characteristics. A significant increase in mortality was observed for patients with hyponatremia or hypernatremia, as compared to ICU patients with a normal serum sodium.

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Zilberberb MD, Exuzides A, Spalding J, et al: Epidemiology, clinical and economic outcomes of admission hyponatremia among hospitalized patients. Curr Med Res Opin 24(6):1601-1608, 2008.

In this retrospective review of more than 100,000 hospital discharges from 39 hospitals in the US, hyponatremia on admission to the hospital was found to be associated with older age and higher number of comorbidities. ICU care, mechanical ventilation, and mortality were all significantly increased among patients with admission hyponatremia.

CHAPTER 85

Thyroid and Adrenal Disorders in the Intensive Care Unit

Alisha N. Wade ■ Kolin Hoff

Abnormalities in thyroid and adrenal function tests are commonly seen in critically ill patients in the intensive care unit (ICU). These may reflect endocrine dysfunction that requires intervention or a physiologic adaptation to illness.

Assessing Thyroid Function in the Critically Ill Patient

Thyroid-stimulating hormone (TSH) is the most sensitive marker of thyroid function except when there is pituitary dysfunction. The thyroid hormones thyroxine (T4) and triiodothyronine (T3) circulate in the blood bound to binding proteins which may be decreased in illness because of decreased hepatic synthesis that, in turn, can result in decreased *total* T4 and T3 concentrations. Assessment of thyroid function in the ICU should be considered only when thyroid dysfunction is suspected to be contributing to the illness. TSH, total T4 and total T3, and T3 uptake with measurement of free T4 (ideally by the direct dialysis method) should be obtained from the same specimen.

The Nonthyroidal Illness Syndrome

The nonthyroidal illness syndrome (NTIS) is an alteration in thyroid function tests seen in patients with acute or chronic illness with no prior history of thyroid dysfunction. Low serum T3 is the most common abnormality in NTIS; however, decreases in TSH and T4 are seen in more prolonged or severe illness. Elevations in reverse T3 (rT3) may also be evident (Figure 85.1).

EPIDEMIOLOGY AND ETIOLOGY

NTIS is seen in up to 75% of hospitalized patients. Whether NTIS represents a physiologic adaptation as the body attempts to reduce energy expenditure or a true pathologic state is uncertain. The decrease in physiologically active T3 results from decreased peripheral monodeiodination of T4. A form of central hypothyroidism also likely exists because of reduced hypothalamic production of thyrotropin-releasing hormone (TRH) with resultant decrease in TSH.

Drugs used in the ICU can also affect both thyroid function and thyroid function tests. Corticosteroids and dopamine decrease both basal TSH secretion and pituitary response to TRH. Corticosteroids also decrease the peripheral conversion of T4 to T3. A number of other drugs commonly used in the ICU can affect the thyroid function or the interpretation of thyroid function tests. Drugs that can cause *hypothyroidism* include lithium, intravenous (IV) iodinated radiographic contrast agents, amiodarone, aminoglutethamide, thalidomide, interferon alpha, and interleukin-2. Drugs that can cause *hyperthyroidism* include iodine and amiodarone, interferon alpha, denileukin diftitox, and interleukin-2.

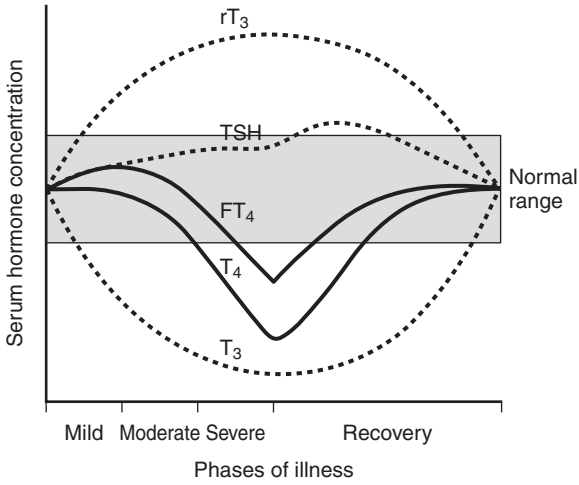


Figure 85.1 Thyroid hormone levels change with course and severity of nonthyroidal illness. FT4, free thyroxine; *r*T3, reverse triiodothyronine; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone. *(From Moore WT, Eastman R: Diagnostic Endocrinology, 2nd ed. St Louis: Mosby, 1996.)*

DIAGNOSIS

TSH is usually suppressed, necessitating differentiation from hyperthyroidism. TSH is low enough to be undetectable in only 7% of NTIS patients (usually those who have received corticosteroids or dopamine). An undetectable TSH therefore suggests hyperthyroidism. Assessment of T4 and T3 levels differentiates between the two conditions, as these will be elevated only in hyperthyroidism (Figure 85.2).

Differentiating between NTIS and *hypothyroidism* is more challenging. An elevation in TSH as high as 20 mIUu/L may be seen during the recovery phase of NTIS. Elevations above 20 mIUu/L occur in only 3% of patients with NTIS and therefore suggest underlying hypothyroidism.

Studies suggest levels of T4 < 4 mcg/dL are associated with mortality risk of 50%, which increases to 80% if levels decrease to 2 mcg/dL. Whether NTIS contributes to this high mortality or merely reflects the severity of underlying illness remains debated. Efforts to supplement T4 and T3 in critically ill patients do not improve outcomes and may be detrimental. Currently no evidence supports thyroid hormone replacement in patients with NTIS. Patients diagnosed with NTIS in the ICU should have an assessment of thyroid function after recovery from their critical illnesses to ensure normalization.

Thyrotoxicosis

ETIOLOGY

Thyrotoxicosis may result from excessive serum concentrations of T4, T3, or both. Primary hyperthyroidism, the usual underlying diagnosis, causes both increased production and release of thyroid hormones; etiologies include Graves disease (diffuse toxic goiter), and functioning thyroid nodule(s) (toxic adenoma or toxic multinodular goiter). Alternatively, hyperthyroidism may result solely from the excessive release of stored thyroid hormone in conditions such as silent thyroiditis, postpartum thyroiditis, and subacute or granulomatous thyroiditis).

Secondary hyperthyroidism is rare and caused by the excessive production of TSH from a pituitary adenoma. In this condition, the thyroid hormone levels are elevated but TSH is elevated or inappropriately normal.

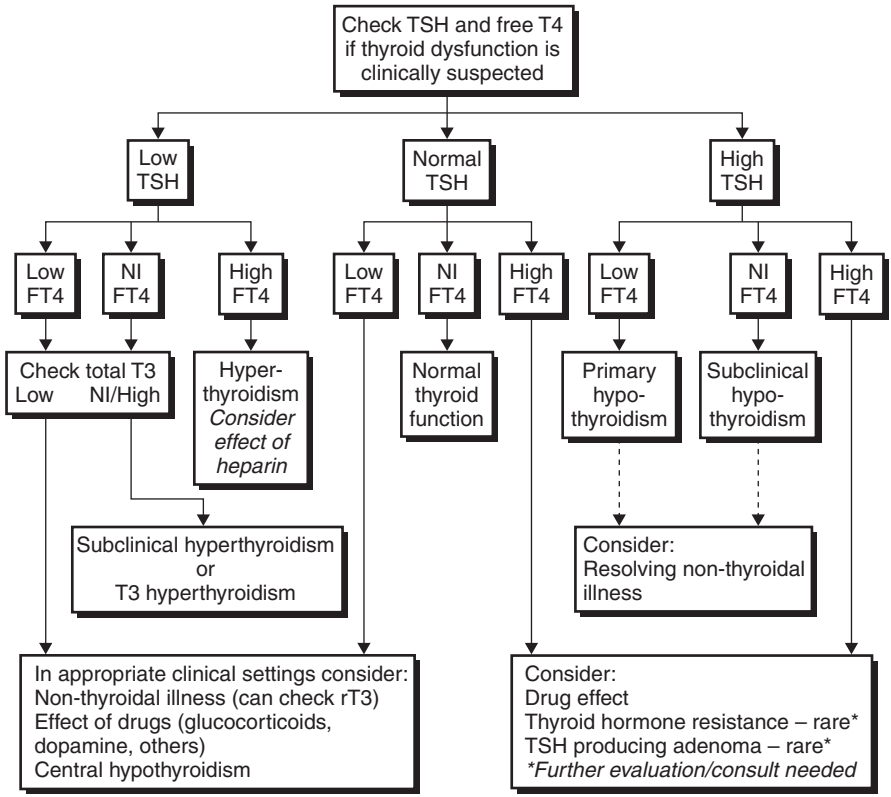


Figure 85.2 Algorithm for evaluation of thyroid disease in critically ill patients. FT4, free T4; NI, normal; rT3, reverse T3; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine.

Other causes of hyperthyroidism include excessive consumption of exogenous thyroid hormone which may be surreptitious. Amiodarone may also cause hyperthyroidism, either by increased thyroid hormone production or a destructive thyroiditis. Additional causes of hyperthyroidism are listed in Table 85.1.

CLINICAL FEATURES

Clinical features of thyrotoxicosis include hyperadrenergic symptoms of anxiety, weight loss, tremor, palpitations, sinus tachycardia, atrial fibrillation, congestive heart failure, and proximal muscle weakness. Patients with Graves disease may have evidence of thyroid-associated ophthalmopathy or a thyroid bruit. Elderly patients may present with *apathetic* thyrotoxicosis with symptoms of apathy and depression.

DIAGNOSIS

Thyrotoxic patients have a decreased TSH (often undetectable) and increases in serum T4 and/or T3. Approximately 1% of patients will have isolated T3 thyrotoxicosis. A 24-hour radioactive iodine (RAI) thyroid uptake/scan or a pertechnetate scan will differentiate hyperthyroidism caused by increased hormone production from increased hormone release or exogenous intake. In

TABLE 85.1 ■ **Causes of Hyperthyroidism**

Common Causes	Underlying Etiology	Diagnostic Features
Graves disease	Thyroid-stimulating immunoglobulin (TSI) binds to and stimulates the thyroid	Increased thyroid radioactive iodine uptake with diffuse uptake on scan, positive thyroperoxidase antibodies; raised serum thyroid-stimulating immunoglobulin; diffuse goiter; ophthalmopathy may be present
Toxic adenoma	Monoclonal autonomously secreting benign; thyroid tumor	Normal to increased thyroid radioactive iodine uptake with all uptake in the nodule on scan; thyroperoxidase antibodies absent
Toxic multinodular goiter	Multiple monoclonal autonomously secreting benign thyroid tumors	Normal to increased thyroid radioactive iodine uptake with focal areas of increased and reduced uptake on scan; thyroperoxidase antibodies absent
Exogenous thyroid hormone	Excess exogenous thyroid hormone	Low to undetectable thyroid radioactive iodine uptake; low serum thyroglobulin values
Painless postpartum lymphocytic thyroiditis	Autoimmune lymphocytic infiltration of thyroid with release of stored thyroid hormone	Low to undetectable thyroid radioactive iodine uptake; thyroperoxidase antibodies present; occurs within 6 months after pregnancy
Painless sporadic thyroiditis	Autoimmune lymphocytic infiltration of thyroid with release of stored thyroid hormone	Low to undetectable thyroid radioactive iodine uptake; thyroperoxidase antibodies present
Subacute thyroiditis	Thyroid inflammation with release of stored thyroid hormone; possibly viral	Low to undetectable thyroid radioactive iodine uptake; low titer or absent thyroid peroxidase antibody (TPO Ab)
Iodine-induced hyperthyroidism	Excess iodine	Low to undetectable thyroid radioactive iodine uptake
Drug-induced thyrotoxicosis	Lithium, interferon alpha; induction of thyroid autoimmunity (Graves disease) or inflammatory thyroiditis	Thyroid radioactive iodine uptake elevated in Graves disease or low to undetectable in thyroiditis
Amiodarone-induced thyrotoxicosis	Iodine-induced hyperthyroidism (type I) or inflammatory thyroiditis (type II)	Low to undetectable thyroid radioactive iodine uptake
Thyroid-stimulating hormone (TSH) secreting pituitary adenoma	Pituitary adenoma	Raised serum thyroid-stimulating hormone and alpha-subunit with raised peripheral serum thyroid hormones
Gestational thyrotoxicosis	Stimulation of thyroid gland thyroid-stimulating hormone receptors by human chorionic gonadotropin	Thyroid radioactive iodine uptake contraindicated in pregnancy; first trimester, often in setting of hyperemesis or multiple gestation
Molar pregnancy	Stimulation of thyroid gland thyroid-stimulating hormone receptors by human chorionic gonadotropin	Molar pregnancy
Struma ovarii	Ovarian teratoma with differentiation primarily into thyroid cells	Low to undetectable thyroid radioactive iodine uptake (raised uptake of radioactive iodine in pelvis)
Widely metastatic functional follicular thyroid carcinoma	Thyroid hormone production by large tumor masses	Differentiated thyroid carcinoma with bulky metastases; tumor radioactive iodine uptake visible on whole-body scan

Adapted from Pearce EN: Diagnosis and management of thyrotoxicosis. Br Med J 332:1369-1373, 2006.

the former, uptake will be elevated or normal, whereas in the latter, uptake will be low. RAI uptake may be falsely low in patients who have recently received iodinated contrast or amiodarone. Alternatively, pertechnetate scanning provides qualitative results in a few hours and an intense uptake of pertechnetate is indicative of increased thyroid hormone production. Either method must be interpreted with concurrent thyroid function tests.

Thyroid Storm

EPIDEMIOLOGY AND ETIOLOGY

Thyroid storm is defined as severe, life-threatening thyrotoxicosis and has a mortality rate of 20% to 30%. It may occur in a patient with known thyrotoxicosis or may be the initial presentation. Any cause of hyperthyroidism may lead to thyroid storm. Thyroid storm is usually precipitated by an acute illness or surgery.

CLINICAL FEATURES

In addition to the hyperadrenergic features of thyrotoxicosis, thyroid storm is marked by the presence of fever, heart failure, and alterations in mental status. Abnormalities in hepatic transaminases may also be present. It can be difficult to distinguish thyroid storm from thyrotoxicosis, and a point-based system has been developed to assist in making the distinction (Table 85.2).

TREATMENT

Treatment of thyroid storm is multifaceted, with therapy simultaneously directed at stopping the production, release, and peripheral action of thyroid hormones. Concurrent conditions such as heart failure or atrial fibrillation should be managed aggressively and precipitating factors should be identified and treated.

The thionamides propylthiouracil (PTU) and methimazole (MMI) are used to reduce thyroid hormone synthesis. PTU is typically the drug of choice, reducing production of T4 in addition to blocking peripheral conversion of T4 to T3. PTU is typically given in a dose of 200 to 300 mg every 4 hours orally, via nasogastric tube or rectally.

MMI, which has a longer half-life than PTU, may also be used. MMI is usually initially given in a dose of 20 to 30 mg every 6 hours. Either PTU or MMI may be dissolved in pH-adjusted isotonic saline and filtered by the hospital pharmacy for intravenous administration. Severe but fortunately rare side effects of these drugs include agranulocytosis, liver toxicity, and vasculitis.

Iodine may be used to block the release of preformed thyroid hormone and thus complement the action of thionamides. Supersaturated potassium iodide (SSKI), given as five drops every 6 hours, diluted in juice or water and given orally or via nasogastric tube. SSKI may be given rectally. Typically thionamides are given prior to iodine to prevent iodine from being used as a source for new thyroid hormone production.

Options for reducing peripheral conversion of T4 to T3, in addition to PTU, include oral iodinated contrast (not available in the United States) and glucocorticoids. The adrenergic manifestations of thyroid storm can be treated with beta-blockers as tolerated by cardiac function. In some cases plasmapheresis has been used to lower thyroid hormone levels.

Supportive therapy to treat other manifestations should be employed. Acetaminophen is the preferred agent to treat fever; aspirin should be avoided, as salicylates can cause the release of thyroid hormone from its binding proteins.

TABLE 85.2 ■ **Diagnostic Criteria for Thyroid Storm**

Criterion	Points
Precipitant History	
Negative	0
Positive	10
Hyperthermia	
99–99.9° F	5
100–100.9° F	10
101–101.9° F	15
102–102.9° F	20
103–103.9° F	25
≥ 104° F	30
Tachycardia	
99–109 beats/min	5
110–119 beats/min	10
120–129 beats/min	15
130–139 beats/min	20
≥ 140 beats/min	25
Atrial Fibrillation	10
Heart Failure	
Pedal edema	5
Bibasilar rales	10
Pulmonary edema	15
CNS Effects	
Agitation	10
Delirium, psychosis, extreme lethargy	20
Seizure or coma	30
Gastrointestinal or Hepatic Dysfunction	
Diarrhea, nausea, vomiting, abdominal pain	10
Unexplained jaundice	20

Score: 45 or higher: suggestive of thyroid storm; 25 to 44: supports the diagnosis; under 25: thyroid storm is unlikely.
Adapted from Burch HB, Wartofsky L: Life-threatening thyrotoxicosis: thyroid storm. Endocrinol Metab Clin North Am 22:263-277, ix, 1993.

Myxedema Coma

EPIDEMIOLOGY AND ETIOLOGY

Myxedema is a life-threatening form of hypothyroidism with a mortality risk near 50%. Typically, there is a prior history of hypothyroidism and noncompliance with thyroid hormone replacement. A precipitating event such as exposure to a cold environment, infection, stroke, metabolic derangements, or drugs (opioids or sedatives) often precedes the condition.

CLINICAL FEATURES

Features of myxedema coma include grossly impaired cognitive function and impaired state of consciousness, though not typically coma. Psychosis may also be a presenting feature.

Hypothermia, hypoxemia, hypercapnia, hyponatremia, hypoglycemia, and seizures also may be present. Cardiovascular complications include decreased cardiac output and cardiac contractility, bradycardia, hypotension, and pericardial effusion.

DIAGNOSIS

The diagnosis is based on history and physical findings as well as laboratory evidence of an elevated TSH and low T4. Of note, however, up to 5% of patients presenting with myxedema may have central hypothyroidism and therefore a normal or low TSH.

TREATMENT

Treatment of myxedema coma involves replacement of thyroid hormones and supportive measures. The dosing regimen and type of thyroid hormone (T3, T4, or both) to be replaced remain controversial as there are few randomized controlled trials to guide therapy. Intravenous administration of T4 is preferred, as gastric absorption is often impaired. T4 (levothyroxine sodium) is typically given in a dose of 200 to 400 mcg as a loading dose and then 1.6 mcg/kg daily. The lower end of the dose spectrum should be used in patients who are elderly, have coexisting ischemic cardiac disease, or have low body weight. T3 (liothyronine sodium) may also be given due to faster onset of action although the benefit is uncertain. If T3 is used, the daily T4 dose may be decreased by 50%. T3 may be given as a loading dose of 5 to 20 mcg and then 2.5 to 10 mcg every 8 hours. High T3 serum levels should be avoided. Once stabilized maintenance therapy with oral T4 should be instituted.

Concomitant adrenal insufficiency must be considered in patients with myxedema, as thyroid hormone replacement in such patients can precipitate an adrenal crisis. An approach is to treat empirically with hydrocortisone until normal adrenal function has been confirmed. Hypothermia may be treated by gentle passive rewarming with a heated blanket to avoid vasodilatation induced by excessive warmth.

Adrenal Dysfunction in the ICU

Adrenal insufficiency is the most common form of adrenal dysfunction in the ICU. Hypercortisolism may result in an immunocompromised state and complicate critical illness, but a detailed discussion of this problem is beyond the scope of this chapter.

Adrenal insufficiency in critical illness may be divided into two categories. The first category includes patients who present with hemodynamic instability as the result of primary or secondary adrenal insufficiency that may have previously been undiagnosed. The second category includes patients who develop critical illness–associated corticosteroid deficiency, which is also known as "relative" adrenal insufficiency.

Preexisting Adrenal Insufficiency

The adrenal gland is composed of the adrenal cortex and medulla, which are anatomically and functionally distinct. The medulla is the inner part of the gland and it produces catecholamines. The cortex has three layers surrounding the medulla. These are (1) the zona glomerulosa (which produces aldosterone), (2) the zona fasciculata, and (3) the zona reticularis. The latter two function as a unit and produce cortisol and androgens. In primary adrenal insufficiency, the adrenal glands are destroyed or dysfunctional, resulting in deficiency of all adrenocortical hormones. In secondary adrenal insufficiency, pituitary and hypothalamic dysfunction result in deficiencies of adrenocorticotropic hormone (ACTH) and corticotrophin-releasing hormone

(CRH) with consequent reduction in the secretion of cortisol but no effect on the production of aldosterone.

EPIDEMIOLOGY AND ETIOLOGY

Primary adrenal insufficiency or Addison disease has a reported prevalence of 35 to 140 per million. Common causes of adrenal insufficiency are listed in Box 85.1. The most common cause is autoimmune adrenalitis, although in critically ill patients, infectious causes such as tuberculosis (TB) and cytomegalovirus (CMV) should be of particular concern in immunocompromised patients. Bilateral adrenal hemorrhage (also known as the Waterhouse-Friderichsen syndrome) is also an important cause of adrenal insufficiency in the critically ill patient who may be anticoagulated or coagulopathic, such as occurs in sepsis-associated disseminated intravascular coagulation (DIC). Exogenous glucocorticoid use is the most common cause of secondary adrenal insufficiency, but tumors or infiltrative disorders of the hypothalamus or pituitary can also result in secondary insufficiency.

CLINICAL FEATURES

Acute adrenal crisis may occur in patients with known adrenal insufficiency or may be the initial presentation. Acute adrenal crisis may be precipitated by infection, trauma, surgery, dehydration, nonadherence to steroid therapy, or failure to increase maintenance steroid doses in times of physical stress. It manifests as hypotension and shock refractory to volume resuscitation, fever, nausea, vomiting, weakness, and altered mental status. Hypoglycemia may also be present. In patients presenting with apparent adrenal crisis, evidence of chronic adrenal insufficiency should be sought. This includes a history of weakness, fatigue, weight loss, abdominal pain, chronic gastrointestinal disturbances, and, on physical examination, hyperpigmentation. Note that in

BOX 85.1 ■ Selected Causes of Adrenal Insufficiency

Primary Adrenal Insufficiency

- Autoimmune adrenalitis (isolated or with associated polyendocrinopathy)
- Infections (e.g., tuberculosis, CMV, HIV/AIDS)
- Metastatic disease
- Bilateral adrenalectomy
- Bilateral adrenal hemorrhage (Waterhouse-Friderichsen syndrome)
- Drug-induced (e.g., ketoconazole, etomidate)
- Idiopathic
- Adrenoleukodystrophy and other congenital disorders

Secondary Adrenal Insufficiency

- Pituitary or hypothalamic tumor
- Pituitary irradiation
- Pituitary surgery
- Pituitary/brain surgery
- Pituitary infections/inflammatory disorders
- Pituitary hemorrhage or necrosis (e.g., postpartum, or peripartum)
- Interruption of chronic glucocorticoid therapy

CMV, cytomegalovirus; HIV/AIDS, human immunodeficiency virus.
Adapted from Bouill on R: Acute adrenal insufficiency. Endocrinol Metab Clin North Am 35:767-775, 2006.

patients with secondary adrenal insufficiency, hyperpigmentation is absent as ACTH secretion is deficient.

DIAGNOSIS

Laboratory findings in primary adrenal insufficiency include lymphocytosis and eosinophilia, hyperkalemia and hyponatremia (both of which result from hypoaldosteronism), and hypoglycemia (which results from cortisol deficiency). Laboratory findings are similar in secondary adrenal insufficiency, although hyperkalemia is usually absent and hyponatremia is due to a loss of negative feedback on arginine vasopressin rather than aldosterone deficiency.

Diagnosis is based on cortisol concentrations and the response to an ACTH stimulation test. An early morning cortisol of 18 mcg/dL or higher indicates normal adrenal function; likewise, a random cortisol concentration of 15 mcg/dL or more also suggests adequate adrenal reserve. Adequate reserve is indicated if the cortisol concentration is 18 to 20 mcg/dL when drawn 30 to 60 minutes after the administration of 250 mcg of ACTH intravenously. A blood sample for measuring ACTH concentration should be drawn at the same time as the random cortisol to assist in distinguishing between primary and secondary insufficiency. Of important note, the 250-mcg ACTH stimulation test may not detect partial or recent secondary adrenal insufficiency. This may be diagnosed using the 1-mcg ACTH stimulation test or other more specialized stimulation tests that are beyond the scope of this chapter. In patients treated with chronic glucocorticoid therapy who present with adrenal crisis, there is little utility in testing the hypothalamic-pituitary-adrenal (HPA) axis, as endogenous cortisol and ACTH secretion will be suppressed. These patients should be treated with stress dose steroids as outlined later.

If acute adrenal insufficiency is suspected clinically, treatment should be instituted immediately and not delayed while the diagnosis is confirmed. In addition to volume resuscitation and identification and treatment of precipitating factors, glucocorticoid replacement should be initiated immediately with 100 mg of intravenous (IV) hydrocortisone. If subsequent assessment of the HPA axis is a consideration, an initial IV dose of dexamethasone 4 mg (roughly equivalent to 100 mg of hydrocortisone in its glucocorticoid activity) may be given as this does not interfere with the subsequent cortisol assay. After the requisite blood tests are performed, a glucocorticoid replacement regimen of hydrocortisone 100 mg IV every 6 hours for the first 24 hours should be initiated and then tapered to 50 mg every 6 hours once the patient has stabilized. This dose can then be tapered to hydrocortisone 20 mg in the morning and 10 mg in the afternoon by the fourth or fifth day of treatment, provided the patient is stable. Long-term maintenance regimens may use hydrocortisone (or an equivalent glucocorticoid) of less than 30 mg daily. In patients with primary adrenal insufficiency, 0.05 to 0.1 mg of fludrocortisone orally should be added when the total daily dose of hydrocortisone decreases to less than 50 to 60 mg; above this dose, hydrocortisone provides adequate mineralocorticoid activity.

Patients with known or confirmed primary adrenal insufficiency require lifelong glucocorticoid and mineralocorticoid replacement, whereas those with secondary adrenal insufficiency usually require only glucocorticoid therapy. If secondary adrenal insufficiency is due to exogenous glucocorticoid use, gradual steroid tapering may be performed as an outpatient treatment.

Adrenal crisis may be prevented by adherence to prescribed adrenal replacement therapies. Patients should obtain medical alert bracelets and also be advised to increase their maintenance steroid dose to two to three times their daily dose in times of illness or injury. If they are unable to tolerate oral steroids because of gastrointestinal upset, they should seek medical care. Physicians should be aware of the need for supraphysiologic steroid doses (i.e., stress doses) in patients undergoing surgery. Similarly, all critically ill patients with known adrenal insufficiency,

regardless of their hemodynamic status, should receive high-dose glucocorticoid therapy until clinically stable.

Critical Illness–Related Corticosteroid Insufficiency (Relative Adrenal Insufficiency)

ETIOLOGY AND EPIDEMIOLOGY

Critical illness–related corticosteroid insufficiency (CIRCI), formerly known as relative adrenal insufficiency, is defined as a cortisol concentration inadequate for the severity of illness. It occurs in approximately 20% of critically ill patients and in 50% to 60% of patients with septic shock. It is considered to be a reversible condition caused by proinflammatory mediators. CIRCI results from both inadequate production of cortisol (likely the result of a combination of factors including reduced production of CRH, ACTH, and cortisol due to various factors including cytokine-mediated HPA axis dysfunction and drug-induced adrenal dysfunction) and increased tissue resistance to cortisol.

DIAGNOSIS

CIRCI should be suspected in any critically ill patient who has hypotension requiring vasopressor support or acute lung injury requiring ventilator support. However, the diagnosis is challenging for several reasons. Free cortisol is responsible for the physiologic function of the hormone, and in critical illness, total cortisol does not accurately reflect free cortisol. This is due to the reduction in cortisol binding globulin in severe illness and the consequent increase in the free cortisol fraction. There are, however, no widely available commercial assays for free cortisol.

The proposed diagnostic criteria of a random total cortisol level < 10 mcg/dL and a change in total cortisol of < 9 mcg/dL in response to 250 mcg of ACTH remain debatable. Some evidence suggests that patients with an ACTH response of < 9 mcg/dL increase in total cortisol have a poorer prognosis. However, the ACTH stimulation test assesses the response of the adrenal gland, but does not evaluate whether the HPA axis is intact or how the HPA axis responds to other stressors.

TREATMENT

Because of diagnostic limitations, glucocorticoid therapy in patients who are most likely to benefit, such as those with refractory septic shock, and the acute respiratory distress syndrome (ARDS), should be based on clinical criteria rather than the results of adrenal function testing. Examination of the available data suggests that 50 mg of hydrocortisone administered intravenously every 6 hours for a minimum of 7 days followed by a taper, speeds resolution of septic shock, but the effect on mortality is uncertain. The duration of therapy is also uncertain, with some studies suggesting a minimum of 5 days followed by a taper and others suggesting continuation of steroid therapy as long as vasopressor support is required. The use of fludrocortisone at a dose 50 mcg daily in these patients is optional. Although controversial and not recommended for routine therapy, methylprednisolone therapy has improved gas exchange in some patients with ARDS that has persisted for 1 to 2 weeks (Chapter 73). The role of adrenal function testing and the utility of glucocorticoid treatment in other critically ill patients remain unclear and require further investigation.

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CHAPTER 86

Perioperative Approach to the High-Risk Surgical Patient

Clifford S. Deutschman ■ Jason C. Brainard

The changes in cellular and biochemical functions that accompany and follow major surgery differ from most others encountered in medical practice. Fortunately, the response to injury follows a predictable patterned response trajectory. These differences in normal homeostasis and the "stress" response become even more important clinically when the patient undergoing surgery is "high risk." High-risk patients are those with preexisting conditions, such as comorbidities or advanced age, that markedly alter their physiologic reserves.

Stress Response to Acute Injury

Acute injury results in a characteristic biphasic set of physiologic and metabolic changes, collectively described as the stress (or inflammatory) response (Figure 86.1). The initial period, which Cuthbertson termed the *ebb phase* in his original description, is associated with decreased cardiac output, a reduction in blood flow to organs other than the brain and central nervous system (CNS), hypothermia, and an overall decrease in the resting energy expenditure (REE). In modern parlance this is a stage of *shock*. As is most often the case with shock, the transition from the ebb phase is rapid when adequate resuscitation is provided. The subsequent period, or *flow phase,* is characterized by fever, an increase in blood flow to most tissues, and an increased REE. Virtually all variables associated with acute inflammation peak on or about postinjury day 2 and then decline to baseline by postinjury day 6 to 7 (Table 86.1). Deviations from this expected pattern indicate the influence of preexisting medical conditions or postoperative complications.

HYPERMETABOLIC PHASE

The increase in energy expenditure (hypermetabolism) that characterizes the flow phase reflects the initiation of processes to repair damaged tissue. The increase is driven primarily by the metabolic activities of inflammatory cells. These cells are obligate glucose users. A continuous supply of glucose is provided by enhanced hepatic gluconeogenesis and glycogenolysis. Skeletal (somatic) and visceral (smooth) muscles are catabolized into amino acids to be used as substrate for the synthesis of structural proteins and enzymes. The energy needs of other organs are primarily met by the oxidation of fatty acids. This global increase in metabolism is reflected in a rise in REE, oxygen consumption, and carbon dioxide production. In the flow phase, peripheral vascular tone decreases and cardiac output increases to provide flow to injured tissue and deliver nutrients to muscle and the liver. Minute ventilation rises in proportion to the increase in carbon dioxide production, keeping $Paco_2$ in the normal range. However, vascular dilation and capillary

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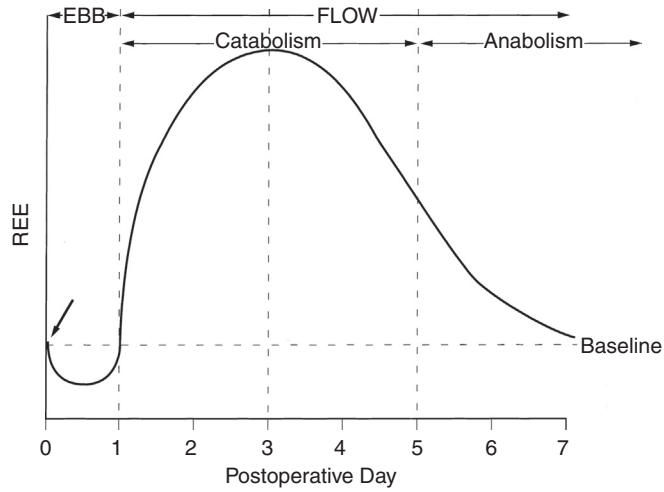


Figure 86.1 Changes in resting energy expenditure (REE) over time following injury. Other "stress" indicators follow a similar time course (see text and Table 86.1). The arrow indicates onset of injury or surgical procedure.

TABLE 86.1 ■ **Increases in Organ System Parameters after Major Surgery**

Organ System	Parameter
Cardiovascular	Cardiac output index
	Heart rate
	Systemic vascular resistance
Pulmonary	Minute ventilation
	CO_2 production ($\dot{V}_{CO2}$)
	Work of breathing
Nutritional-metabolic	Resting energy expenditure (REE)
	Inflammatory mediators
	Cytokines
	Interleukins
	Tissue necrosis factor
	Oxygen consumption ($\dot{V}_{O2}$)
	Lipolysis (respiratory quotient)
	Gluconeogenesis
Neuroendocrine	Catecholamines
	Corticosteroids
	Renin-angiotensin-aldosterone

The time course of these changes parallels the response trajectory described in Figure 86.1.

recruitment are insufficient to support the delivery of substrate to damaged tissue. Most injured tissue is essentially avascular, and substrate delivery is primarily a function of diffusion across a concentration gradient into the interstitium. To increase substrate delivery to a wound, capillaries become "leaky" and fluid is lost to the extravascular compartment. This results in *intravascular* fluid depletion. To compensate there is an increase in renal salt and water retention and fluid translocation from the intracellular compartment (Figure 86.2).

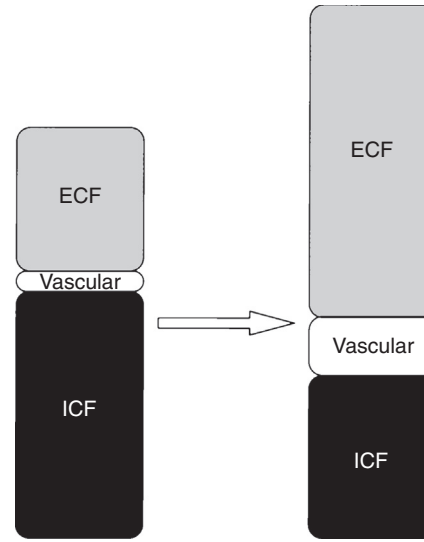


Figure 86.2 Schematic changes in fluid compartments following major surgery with postoperative exogenous fluid therapy. Note that an obligatory expansion of the extracellular fluid (ECF) compartment occurs, and this must be supported by exogenous fluid administration to limit depletion of intravascular or intracellular fluid (ICF) volumes.

Unchecked, the hypermetabolic process would eventually result in death. By the fourth to fifth postoperative day, however, likely as a direct result of neovascularization, there is restoration of blood flow to the wound and enhanced delivery of substrate that reverse the hypermetabolic process. This subdivision of the hypermetabolic phase was first recognized by Francis Moore. He called the pre-neovascularization period the *catabolic phase* (reflecting the catabolism of endogenous protein and loss of cellular water) and the post-neovascularization period the *anabolic phase*.

The anabolic phase is characterized by restitution of body cell mass; movement of water, potassium, magnesium, and phosphate back into cells; vasoconstriction; and mobilization of interstitial fluid. Clinically, there is a brisk diuresis, resolution of anasarca as the capillary leak resolves, and a decrease in serum levels of potassium, magnesium, and phosphate (resulting in the need for replacement therapy). The time required to restore the tissue depletion that results from catabolic changes is proportional to the degree of injury and typically takes weeks to months after major surgery or trauma.

The hypermetabolic *flow phase* is driven by the energy required for tissue repair. To date, attempts to prevent this phase have been ineffective. For example, the use of epidural anesthesia to block the sympathetic nervous system delays the onset of catabolism, but once the anesthetic is removed, hypermetabolism begins. Similarly, drugs such as beta-adrenergic blockers (which limit a patient's ability to achieve the peak metabolic and physiologic changes of the hyperdynamic phase) can reduce the peak hypermetabolic response but subsequently prolong its duration.

POSTOPERATIVE ISSUES

Concurrent diseases may have their greatest impact by limiting responses during the hyperdynamic phase. The magnitude of these changes depends on the extent of the initial injury as well as on preexisting diseases (Table 86.2). Three important factors have an impact on the patient's ultimate outcome. The *first factor* is the ability of the patient to mount a hypermetabolic response. In some cases, this requires high levels of hemodynamic support. In others, however, the intensive care unit (ICU) physician's role in management is simply to support the hypermetabolic response, particularly by replacing ongoing fluid losses (especially those lost into the "third space"). This

TABLE 86.2 ■ **Disease States Compromising the Extent of the Hyperdynamic Response**

Organ System	Disease
Cardiovascular	Coronary artery disease
	Myocardial pump dysfunction
	Valvular heart disease
	Peripheral vascular disease
	Rhythm disturbance with reduced cardiac output
Pulmonary	Emphysema
	Restrictive lung disease
	Reactive airway disease
Neuromuscular	Altered mental status, confusion
	Stroke
	Myopathies
	Myasthenia gravis
	Muscular deconditioning
Gastrointestinal: metabolic	Nutritional deficiencies
	Malabsorption syndromes
	Renal insufficiency
	Hepatic synthetic disorder, cirrhosis
Endocrine	Addison disease (or inadequate adrenal cortical function resulting from chronic corticosteroid use)
	Hypothyroidism

allows the cardiovascular system to become hyperdynamic, which, in turn, supports blood flow and oxygen delivery to the wound and major organ systems such as the liver and kidneys.

The *second factor* is the ability of the ICU clinician to recognize when the patient's response deviates from the expected pattern. The patient who remains hypermetabolic—that is, manifesting neither a brisk diuresis nor requiring replacement of potassium, magnesium, or phosphate by postoperative day 6 is not following the expected response trajectory. He or she has an ongoing hypermetabolic process that reflects a complication, most often infectious. The *third factor* is the extent to which preexisting disease and therapy for those disorders alter the ability of the patient to tolerate hypermetabolism or to resolve the hypermetabolic state. For example, beta-blockade may alter the patient's ability to become hypermetabolic, thus limiting or prolonging the expected response.

PREOPERATIVE ISSUES: PREPARING THE HIGH-RISK PATIENT FOR SURGERY

Response to surgical trauma should be viewed within the context of the stress response. In this paradigm, the ebb phase is initiated by the induction of anesthesia. This leads to venous pooling, a decrease in cardiac output secondary to a loss of preload and a decrease in blood flow to all systems other than the CNS. This may be exacerbated by intraoperative blood loss, insensible fluid losses, and under-resuscitation. If fluid resuscitation is appropriate, the transition to hypermetabolism will begin intraoperatively. This imposes an additional need for fluid to accommodate the increased perfusion and capillary leak that are characteristic of the flow (hypermetabolic) phase. Preparing the high-risk patient for surgery requires anticipating this pattern and appreciating how the patient's physiologic limitations may interfere with the fluid requirements imposed by hypermetabolism.

The hallmark of this perioperative approach to the high-risk surgical patient is to ensure the optimal functioning of physiologic systems when they are activated in response to surgical stress. Many surgical interventions can be anticipated well in advance, allowing time to plan a course of action. When dealing with a critically ill patient, however, only hours rather than days may be available for this preparation.

Fortunately, even with limited time, a great deal can be done to support the cardiopulmonary and metabolic reserves of the patient preoperatively. Key interventions are (1) restoration of fluid volume stores, (2) correction of important electrolyte abnormalities, (3) limitation of exogenous catecholamine administration, (4) maintenance of normothermia, (5) correction of reversible impairment of pulmonary mechanics, particularly bronchospasm, and (6) initiation of other exogenous therapy, such as mechanical ventilation and metabolic support, when indicated.

Specific Perioperative Interventions

CORRECTING VOLUME DEFICITS

The preoperative management of the critically ill or high-risk surgical patient begins with ensuring adequate *intravascular*, *interstitial*, and *intracellular* fluid volumes. Because the delivery of substrate for repair of damaged tissue is accomplished in part by the development of capillary leak, fluid shifts from the intravascular and intracellular compartments into the interstitial compartment occur even in undamaged tissue. As a result, postoperative physiology will be exaggerated in the face of any preexisting deficit in intravascular or intracellular fluid volume. Further, adequate intravascular volume is essential for the development of the hyperdynamic cardiovascular response. Repleting intravascular volume permits the development of an appropriate hemodynamic response without excessive tachycardia and its associated myocardial oxygen demand.

Assessing and achieving proper fluid balance in critically ill patients can be difficult (Chapter 7). This problem is amplified in patients with major preexisting medical disorders (see Table 86.2). Additionally, some patients appear to be in fluid balance or even overloaded when, in fact, a relative intravascular volume deficit exists. For example, the use of diuretics in patients with congestive heart failure or hypertension can lead to total body deficits of water, sodium, and potassium. These may result in an inability to mount an adequate postoperative hyperdynamic response.

A number of surgical factors can be expected to exaggerate relative preoperative hypovolemia. Critically ill patients taken to the operating room from the ICU or the emergency department may have unrecognized intravascular volume deficits resulting from infection, fever, or bleeding. Patients receiving bowel preparation agents prior to surgery and those who have been *nil per os* (NPO) may have significant volume deficits upon presentation. The acute venodilatory and anti-inotropic effects of anesthetics can compound the hemodynamic consequences of preoperative hypovolemia, placing the patient at even greater risk. Major drops in blood pressure associated with the induction of anesthesia are often a sign of intravascular fluid depletion.

In short, the safe conduct of surgical intervention and the requirements of postoperative physiology demand that hypovolemia be avoided or rapidly corrected in the preoperative and intraoperative periods.

OPTIMIZING CARDIAC PERFORMANCE

The normal physiologic response to injury requires the development of a hyperdynamic cardiovascular state proportional to the degree of injury. Preexisting myocardial dysfunction may limit a patient's ability to increase cardiac output. Cardiomyopathy leads to a reduction in fixed and augmented stroke volume. In the chronically stressed myocardium, increased catecholamine stimulation results in changes in adrenergic receptor populations. This may decrease the functional response to endogenous or exogenous catecholamines. Increases in cardiac output are therefore primarily accomplished by increases in heart rate.

Patients with coronary artery disease frequently require surgery and may experience postoperative myocardial ischemia and perhaps myocardial infarction and death. Based on the timing of the stress response, it is possible to predict how and when this ischemia occurs. Assuming appropriate fluid resuscitation to ensure development of the hyperdynamic response, the demanded increase in cardiac output may exceed the ability of diseased coronary arteries to supply the amplified myocardial oxygen consumption by postoperative day 2. Not surprisingly, this corresponds in time with the peak incidence of postoperative myocardial infarction.

Several strategies to minimize cardiac ischemia may be employed. These include (1) adequately controlling pain (Chapter 88) to limit increases in heart rate and oxygen utilization; (2) avoiding hypotension, especially diastolic hypotension, via liberal fluid administration to prevent myocardial malperfusion; and (3) preventing increases in heart rate by continuing perioperative beta-adrenergic

blockade. The last, however, alters not just cardiodynamics but also the metabolic response essential to the inflammatory response. This may prolong the catabolic phase. The trade-off, however, is usually acceptable because perioperative myocardial infarction and ischemia are such serious complications.

If intravascular volume is deemed adequate and the patient remains unstable or has evidence of hypoperfusion, ventricular performance must be addressed (Figure 86.3). In general this can be approached in two ways. First, medications to enhance inotropy may be needed. Improved myocardial performance from inotropic support may lead to a more appropriate distribution of blood flow and with it a decrease in impedance to flow. However, most available inotropic agents affect catecholamine receptors and thus enhance impedance, increase heart rate, augment myocardial wall tension, and increase myocardial oxygen demand. Thus, they may amplify rather than improve the problem. An alternate approach is to reduce impedance via dilatation of blood vessels. Vasodilators such as angiotensin-converting enzyme (ACE) inhibitors are known to improve ventricular performance without directly altering myocardial energetics. A treatment that bridges both approaches is the use of phosphodiesterase inhibitors such as milrinone. These agents both prolong isobaric contraction and inhibit vasoconstriction. Importantly, any approach

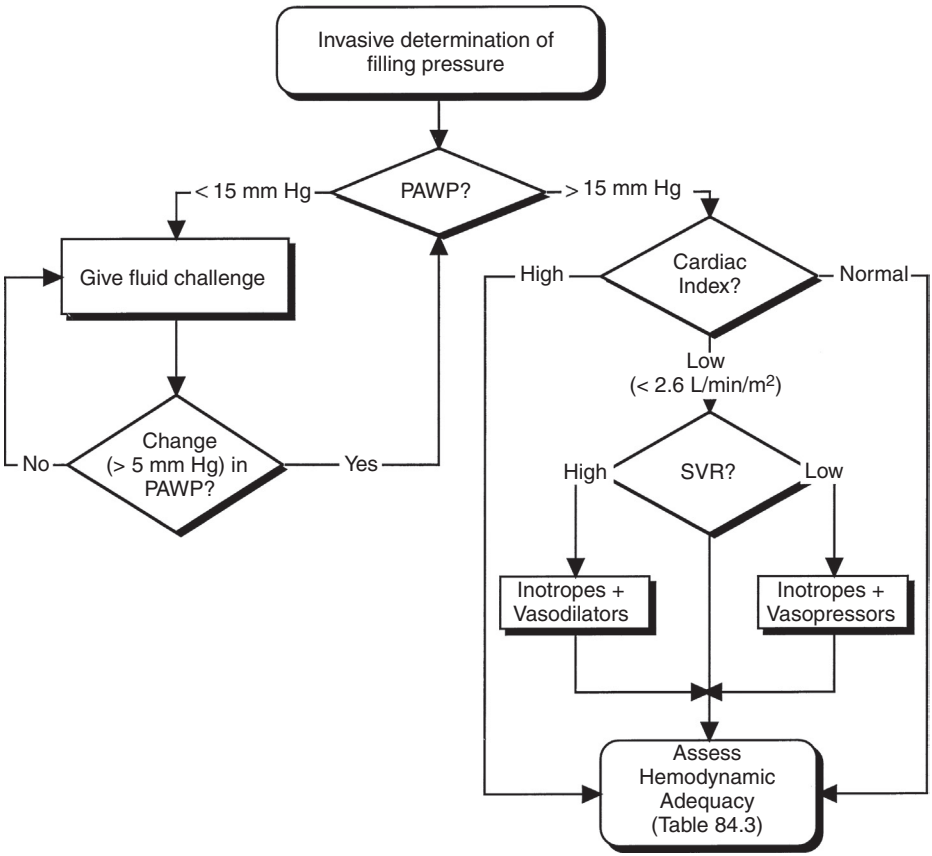


Figure 86.3 Schematic flow diagram illustrating steps in invasive assessment of effective intravascular volume (as represented by pulmonary artery wedge pressure) and adequacy of hemodynamics. PAWP, pulmonary artery wedge pressure; SVR, systemic vascular resistance.

Preoperative tachycardia should prompt a search for contributory factors amenable to correction (pain, hypovolemia, and hypoxia, among others). Any mechanical factor that reduces cardiac compliance or efficiency also limits maximal cardiac performance. Pericardial effusion, tamponade, or trauma-induced decreases in ventricular compliance ("stiff heart") reduce diastolic filling and stroke volume. Arrhythmias may result in uncoordinated atrioventricular activity or an inadequate diastolic interval for ventricular filling. Efforts should be made to stabilize all acute and some chronic arrhythmias to increase cardiac performance.

TABLE 86.3 ■ **Methods to Assess Hemodynamic Inadequacy**

Clinical Parameter	Consistent with Inadequate Hemodynamic Status
Systolic blood pressure	< 90 mm Hg or > 40 mm Hg drop from baseline hypertension
Mean blood pressure	< 60 mm Hg
Slow capillary filling on digits	> 2 sec (> 3 sec in elderly)
Skin appearance	Mottling of skin of lower extremity, livedo reticularis
Urine output	< 30 mL/h
Invasive Parameter	
Cardiac index	< 2.6 L/min/m^2
$Sc\dot{V}_{o2}$ or $S\dot{V}_{o2}$	< 70%

TABLE 86.4 ■ **Use of $\dot{D}o_2/\dot{V}o_2$ and Mixed Venous Oxygen Saturation to Assess Hemodynamic Adequacy**

$\dot{D}o_2/\dot{V}o_2$	Mixed Venous Oxygen Saturation*	Oxygen Extraction	Likely Cardiac Index	Comments
4–5:1	> 75%	Low	Normal/high	If serum lactate level–anion gap is elevated or patient needs inotropes or vasopressors, consider sepsis, liver failure, arteriovenous fistula, adrenal failure, or anaphylaxis. If not, hemodynamics are adequate-to-optimal for $\dot{V}o_2$.
2–3:1	< 70%	Moderate	Low/normal/high	Inconclusive data; consider both extremes while observing trend.
< 2:1	< 50%	High	Low/normal	Inadequate cardiac index for $\dot{V}o_2$ (Chapter 8); increase in $\dot{V}o_2$ may be due to shivering, fever, or major wound healing.

*Assumes Sa_{O_2} = 100%.

may affect the size of the vascular compartment. Thus all available interventions may necessitate administration of additional fluid. Optimal hemodynamics are necessary to perfuse key organ systems and to match oxygen delivery to oxygen consumption (Tables 86.3 and 86.4).

PULMONARY DYSFUNCTION

The postinjury response and the hypermetabolic phase mandate increased oxygen delivery and increased carbon dioxide excretion. This requirement increases the work of breathing and may be tolerated poorly by patients with intrinsic lung disease. Therefore, it is important to identify individuals with baseline hypercapnia or those with severe obstructive airway disease or neuromuscular dysfunction who may experience hypercapnic respiratory failure postoperatively despite normal baseline arterial blood gases.

Preoperative pulmonary care should concentrate primarily on improving reversible conditions. In many cases, patients with bronchospasm will present with appropriately administered combinations of beta-agonists and ipratropium bromide via metered dose inhalers or nebulizers (Chapters 76 and 77). Should this not be the case, optimization prior to the operating room may be beneficial. If bronchospasm persists despite these agents, systemic steroid therapy should be considered. Inhaled steroids are not useful in the acute setting because 2 to 4 weeks of use is required to see benefit. Endotracheal suctioning in intubated patients is logical and should be performed regularly unless contraindications such as bleeding or a recent bronchial anastomosis are present. The value of other forms of therapy is less clear. Studies on perioperative and ICU use of mucolytics have not demonstrated benefit, whereas postural drainage may be physically problematic. Simple methods of pulmonary preparation should not be overlooked. Deep breathing and splinted cough instruction are inexpensive ways to avoid postoperative pulmonary complications. Finally, high-risk patients undergoing elective surgery should be counseled in the strongest possible terms to stop smoking preoperatively. Although smoking cessation for at least 1 month prior to surgery likely yields the greatest benefit, patients should be encouraged to quit smoking at anytime.

MALNUTRITION

Data collected from as long ago as 1936 indicate that a severe nutritional deficit increases perioperative morbidity and even mortality. Studies are less clear, however, on the value of nutritional repletion prior to surgery. It may not be possible to correct metabolic and nutritional deficits acutely in critically ill patients prior to surgery. Postoperatively, hypermetabolism will place additional demands on the nutritionally depleted patient. Postoperative caloric and protein requirements may exceed basal requirements considerably. However, the changes in metabolism discussed earlier limit the value of exogenous glucose to support or replete body cell mass. Thus, empirically increasing calories, especially those delivered as glucose, by some arbitrary factor may result in overfeeding. This, in turn, can increase the demand on the respiratory system by increasing the respiratory quotient ($RQ = \dot{V}_{CO2}/\dot{V}_{O2}$). An RQ greater than 1 often leads to net lipogenesis, a situation that increases CO_2 production and may lead to respiratory failure. Accurate bedside measurements of REE to define nonprotein caloric requirements have been touted to guide therapy, but prospective data are lacking and current methodology may not be useful in critically ill, ventilated patients (Chapter 15).

RENAL DYSFUNCTION

Patients with elevated BUN and creatinine levels should be evaluated for renal, prerenal, or postrenal azotemia, and correctable causes of pre- and postrenal azotemia should be treated (Chapters 82). If the azotemia is found to be based on decreased renal function, electrolytes should be closely monitored and the need for preoperative dialysis should be evaluated. Patients currently receiving renal replacement therapy should be dialyzed on the day prior to scheduled surgery. These patients are likely to be hypovolemic preoperatively and appropriate care, including fluid repletion, should be undertaken prior to and during the induction of anesthesia. Finally, the likely need for postoperative dialysis in the setting of preoperative azotemia should be discussed with the patient and family prior to surgery. Importantly, the possible need for urgent or even emergent dialysis in patients with chronic renal insufficiency or even overt failure should not limit the administration of appropriate amounts of fluid to support hemodynamics and altered metabolism. Similarly, the potential for the development of azotemia does not preclude the provision of appropriate amounts of protein to support metabolism and healing.

Several caveats apply to the assessment of renal function in the critically ill patient. Surgical trauma results in activation of the renin-angiotensin-aldosterone system. As a result, sodium

Patients should be given as much information as possible when a period of postoperative mechanical ventilation is likely. This should include the rationale for its use and reassurance that it is intended as a temporary supportive measure only. Many misunderstandings regarding patient preferences against long-term mechanical ventilation can be avoided by having such discussions with the patient and family prior to surgery. Importantly, the best of intentions may go awry and long-term ventilation and even a surgical airway may become necessary. This requires an equally frank discussion with family and, if possible, the patient. This should include recognition that the practice of critical care medicine remains an inexact science and that physicians' predictions are not always correct.

uptake and water reabsorption increase in the immediate postoperative period. Urinary output then becomes an unreliable indicator of adequate intravascular volume or tissue perfusion. Intraoperative urine output also correlates poorly with postoperative renal function. Conversely, increased solute loads occurring after tissue disruption, absorption of hematoma, perioperative hyperglycemia, or administration of exogenous solutes may result in an artificial elevation in urine output as obligate water loss accompanies excretion of solutes. Finally, the effects of vasoactive agents on afferent and efferent glomerular blood flow and dilution of medullary concentration gradients may change urine flow independent of effective intravascular volume.

Perioperatively, the indiscriminate use of diuretics should be avoided as several studies have confirmed that they do not improve renal function. Once a loop diuretic is administered, urine output becomes even more unreliable for assessing the renal response to physiologic changes. Low or "renal" dose dopamine use is not supported by the literature. Although this agent does increase urine output, it does so by stimulation of D1 receptors on the loop of Henle and the distal convoluted tubule. This increases chloride and water excretion in a manner similar to loop or thiazide diuretics. Dopamine affects glomerular filtration, however, only in so far as it alters blood pressure. Thus, it has no advantage over other vasopressor agents. In fact, dopamine (and, indeed, epinephrine via its strong beta-2 agonist properties) may actually be detrimental because it dilates vessels in skin and skeletal muscle and may divert flow from the splanchnic circulation, including the renal vessels. The relevant variable in assessing renal function is not urine output per se, but the ability of the kidney to handle the increased solute load presented in the postoperative period. Measures of concentrating ability, such as the fractional excretion of sodium or, more simply, the urine sodium, appear to be more reliable in critically ill nonsurgical patients, but their perioperative value is less clear (Chapter 82). The first response to a falling urine output (< 0.5 mL/kg per hour) should always be clinical assessment of intravascular volume and whether it improves after a fluid challenge in the absence of unequivocal signs of volume overload. Even in the setting of high filling pressures, cardiac output and afterload should be optimized before diuretics are given (see Figure 86.3).

ELECTROLYTE ABNORMALITIES (CHAPTER 40)

Hypomagnesemia and hypocalcemia may play a role in depressed cardiac performance in critically ill patients. Hypomagnesemia can contribute to ventricular and supraventricular tachyarrhythmias that are resistant to traditional antiarrhythmic therapy. Magnesium is also required as a cofactor in the enzymatic reactions of the coagulation cascade. Severe hypophosphatemia can impair intracellular generation of high-energy phosphates. Cardiac and respiratory arrest has been reported in association with severe phosphate depletion. Because the risk of normalizing serum phosphate levels is small (if carried out enterally), treatment of documented deficiencies is warranted. In addition, there are few detrimental effects to hypermagnesemia, and it may be quite valuable in suppressing many arrhythmias.

Hypokalemia is often seen preoperatively as a result of diuretic therapy or inadequate replacement of renal or gastrointestinal losses. Although preoperative hypokalemia was associated with cardiac arrhythmias in the past, more recent observations suggest that the risk of a serious rhythm disturbance in patients with chronic hypokalemia is only slight. Because potassium is lost intracellularly as well as extracellularly, the transmembrane gradient may be near normal in states of chronic potassium losses. The rapid correction of chronic mild or moderate hypokalemia may increase the risk of arrhythmias. Delaying urgently needed surgery for hypokalemia in the absence of life-threatening arrhythmias is unwarranted. Conversely, as described earlier, the anabolic phase of the stress response may result in depletion of serum potassium, magnesium, and phosphate as restoration of intracellular mass results in a transfer of these electrolytes into cells. In fact, the depletion may be substantial, often amounting to hundreds of milliequivalents of K+ daily. Under these circumstances, aggressive repletion is warranted.

HEMATOLOGIC AND COAGULATION FUNCTION

Preoperative abnormalities of coagulation may be mild, moderate, or severe. Although severe elevations of prothrombin time (PT) and partial thromboplastin time (PTT) should be corrected, the correction of mild elevations is controversial, with little evidence for excessive bleeding for an international normalization ratio (INR) less than or equal to 1.8. More important are the number of circulating platelets. Although not a risk factor for spontaneous bleeding, platelet counts of 50,000 to 75,000/μL are associated with increased surgical bleeding. Accordingly, preoperative platelet transfusions to achieve counts of 80,000 to 100,000/μL are indicated. Qualitative abnormalities of platelet function alone caused by drugs (aspirin, nonsteroidal anti-inflammatory drugs) or disease (uremia) do not correlate well with excessive surgical bleeding.

Perioperative Invasive Monitoring: When and for How Long?

No invasive monitoring method is without risks. In the case of invasive cardiopulmonary techniques, risk generally falls into two categories. The first is technical and relatively time independent. Examples are arrhythmias, bleeding, or pneumothorax at the time of insertion of central venous and pulmonary artery catheters. The second includes inherent complications of foreign bodies, which are time dependent. The most common of these is catheter-related infection. Some complications—for example, pulmonary artery rupture associated with balloon inflation—fall between these groups. It is axiomatic that, before attempting a procedure in critical care, as in all medicine, the benefit of the procedure must be judged to outweigh its risk.

Intra-arterial catheters are used commonly in procedures associated with significant blood loss and procedures involving rapid fluctuations in blood pressure (for example, pneumonectomy, intracranial aneurysm clipping, pancreatectomy, or surgery on or near major blood vessels). These catheters provide consistent access to arterial blood for respiratory, hematologic, and electrolyte monitoring. Additionally, the variability in the arterial waveform can be used as an adjuvant for assessing intravascular volume.

The placement of central venous catheters and pulmonary artery (PA) catheters for hemodynamic monitoring is controversial, as studies have failed to show improvements in patient outcome. Concern regarding the appropriate use of these devices, as opposed to their mere presence, limits the overall validity of these investigations. Nonetheless, studies indicate that the use of PA catheters in both the operating room and the intensive care unit has declined significantly. It seems prudent to base the decision for invasive central monitoring on specific patient physiology, the nature of the surgery, and the provider's knowledge and understanding of the use of these hemodynamic monitors.

Because postoperative morbidity, especially cardiac morbidity, peaks on the second or third day after operation, it is sensible to continue monitoring the cardiovascular response of the high-risk patient at least through this period. As a practical rule, once invasive monitoring is established, it should be maintained until the hyperdynamic phase is clearly resolving (in the absence of specific indications to stop it earlier) or when the data provided are no longer being used to make treatment decisions.

Conclusion

- Stress response includes the ebb ("shock") and flow (hypermetabolism) phases.
- Patient outcome depends on one's ability to mount and recover from hypermetabolic phase.

- The physician's role is to support the hypermetabolic phase and identify deviations from this process.
- Key interventions include (1) correcting volume deficit, (2) optimizing cardiac and respiratory performance, (3) maintaining and supporting renal function, and (4) ensuring adequate energy supply (nutrition).

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 87

Management of Postoperative and Other Acute Pain

Mitchell D. Tobias ■ Andrew Mannes

Because postoperative pain can be anticipated, it is a unique form of acute pain. It thereby lends itself to the use of preemptive analgesia and offers the potential for complete control. This chapter focuses on the current understanding of mechanisms of pain and practical methods of pain ablation and acute pain management in the intensive care unit (ICU) setting.

Undermedicating Postoperative Pain

Historically, *pro re nata* (prn, as needed) opioids have been administered parenterally in an effort to manage acute postoperative pain. Time has proved this to be a safe method that requires no special equipment or hospital support and with which health care providers are comfortable. Unfortunately, most patients treated in this manner are *not* relieved of pain, and they recall moderate to severe distress postoperatively. Undermedication to treat this pain continues to be a problem.

Although the causes of postoperative undermedication are myriad, the most common reason is a lack of a fundamental knowledge of the pharmacology of commonly employed medications. In one survey of ICU-based physicians and nurses, a large majority of physicians held the misconception that benzodiazepines provided analgesia. Another problem relates to lack of clinical experience for clinicians caring for patients in the ICU. For example, management of postoperative pain is often relegated to the least trained members of the surgical house staff. As the Committee on Advancing Pain Research, Care, and Education of the Institute of Medicine reported:

> *[T]here are strong indications that pain receives insufficient attention in virtually all phases of medical education—the lengthy continuum that includes medical school (undergraduate medical education), residency programs (graduate medical education), and courses taken by practicing physicians (continuing medical education [CME]).*

These barriers to effective pain management are compounded by excessive fears of both patients and staff regarding addiction and side effects of opioids. There is abundant evidence that the extremely subjective nature of pain and bilateral miscommunication also contribute to undermedication. Fears of side effects (particularly respiratory depression) and failure to appreciate the severity of pain have classically led to administration of only 25% of an already over-conservative *prn* prescription.

Finally, there is a lag time in the delivery of prn opioids between when the patient requests pain relief and when he or she actually receives that relief. Typically, a nurse must first respond to a patient's call bell and locate, prepare, and administer the opioid, after which the patient must await the therapeutic effect of the opioid. This lag time becomes even more problematic

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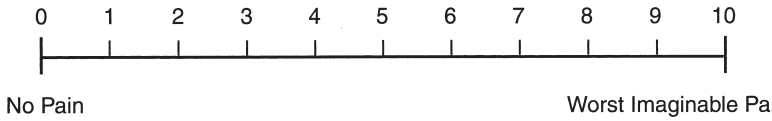


Figure 87.1 Typical visual analog pain scale (VAPS) in which patients are asked to indicate by voice or by pointing where their pain is located on the scale. A score of 3 is usually acceptable in ICU patients.

when, as is typical, the patient does not request relief until the pain is overwhelming. *Pro re nata* administration is more effective if frequent small doses of intravenous (IV) analgesic are immediately available. Indeed, this is the basis of patient-controlled analgesia (PCA).

Assessment of Pain

Pain involves a subjective perception of a sensory stimulus and an emotional reaction to it. The subjective nature of pain renders it difficult to quantify in terms of severity. In conscious patients, this assessment may be made by analysis of a patient's verbal and behavioral expressions. Interpreting these expressions can be challenging in patients with extremely stoic or emotive personalities. In unconscious, sedated, or paralyzed patients, vital signs and provocative tests must be relied on. Assessment of pain in the unresponsive patient may be undertaken by (1) noting changes in continuously monitored arterial pressure and pulse rate in response to palpation or percussion of injury or incision sites and (2) measuring tidal volume and respiratory rate in an intubated patient. In awake and cooperative patients, bedside spirometry performed before and after analgesic administration can provide valuable insights into the therapeutic efficacy of pain management strategies.

In alert, conscious patients, pain can be objectively assessed using a visual analog pain scale (VAPS) (Figure 87.1). This easy-to-understand system helps to avoid misinterpretation. Patients generally do not choose values on either extreme, and a VAPS score of 3 (or less) is considered to represent acceptable pain control in an ICU setting. There is usually always some patient discomfort, even if unrelated to the surgery (e.g., intravenous catheters, nasogastric tube, bed-bound status, tape, and so on). The choice of values on one extreme or the other of the VAPS generally implies a stoic or emotive personality.

Rationale for Using Preemptive Analgesia

Effective preoperative analgesia often decreases postoperative pain in a manner that exceeds expectations based solely on the pharmacodynamics and pharmacokinetics of the drugs administered. Studies support a concept of postinjury *peripheral* and *spinal* nerve hypersensitization and spinally mediated *neuroplasticity* following pain perception (nociception). Neuroplasticity implies that the central nervous system and the dorsal horn cells adapt in response to noxious stimulation. For example, repetitive stimulation of small pain fibers produces a progressive increase in action potential discharge (wind-up) and a prolonged increase in the excitability of spinal neurons with which they synapse. Central sensitization predisposes dorsal horn nociceptive neurons to respond to the input of normally innocuous A_b afferent fibers. Spinal sensitization seems dependent upon *N*-methyl-D-aspartate acid (NMDA) receptor stimulation and may be prevented by *N*-methyl-D-aspartate acid receptor antagonists administered before or after the peripheral injury. Small clinical studies have elucidated improved pain scores, decreased regions of perceived hyperalgesia, and decreased opioid requirements up to 6 months postoperatively following rectal carcinoma resection through the use of subanesthetic doses of ketamine via continuous infusion during anesthesia for surgery.

TABLE 87.1 ■ **Recommendations for Intravenous Opioid Patient-Controlled Analgesia (PCA)**

Opioid	Bolus	Lockout	Basal Infusion
Fentanyl	20–50 μg	5–10 min	20–100 μg/h
Hydromorphone	0.1–0.5 mg	5–15 min	0.2–0.4 mg/h
Morphine	0.5–3 mg	10–20 min	1–10 mg/h

The prevention of central sensitization can be achieved through the preemptive use of local anesthetics, opioids, and, to a degree, nonsteroidal anti-inflammatory drugs. Interventions *following* injury or surgery are much less effective. One should note that volatile anesthetics neither provide preemptive analgesia nor prevent central sensitization.

Methods of Controlling Postoperative Pain

PATIENT-CONTROLLED ANALGESIA

Patient-controlled analgesia (PCA) is a modality designed to accommodate an approximate fourfold variation in opioid analgesic requirements among patients for the same noxious stimulus. PCA permits patients to treat their pain by direct activation of a microprocessor-controlled programmable infusion device that administers intermittent predetermined aliquots (demand doses) of analgesic intravenously (IV). Often there is concurrent continuous IV infusion of the same drug (basal rate) delivered by the same device.

The demand dose is immediately responsive to the patient's perceived pain and permits titration of analgesics to the minimal effective analgesic concentration, thus reducing periods of excessive pain or sedation. Patients act as their own "nocistat" with frequent small prn (demand) boluses. Analgesic administration is reduced to a simple feedback loop: The patient's request for analgesia is rapidly honored by the PCA pump, which minimizes the "lag time." In effect, PCA optimizes the traditional prn opioid cycle. The frequency of administration of the demand dose is determined by a preset interval (lockout time), which is predicated on the pharmacokinetics of the medication being used (Table 87.1).

Compared with patients receiving traditional prn opioids, patients using IV PCA achieve earlier ambulation, better cooperation with physiotherapy, and shorter ICU and hospital lengths of stay.

Dexmedetomidine

Dexmedetomidine is very useful for ICU procedures because of its sedative and analgesic properties. In contrast to the gamma-aminobutyric acid (GABA) agonists commonly employed for sedation in a postoperative ICU stay (benzodiazepines), dexmedetomidine yields sedation with easy awakening and a synergy with opioid analgesics (sparing effect) through alpha 2 CNS receptor agonist effects. In this regard, dexmedetomidine is about eight times as potent, has more alpha 2 specific effects, and has a shorter half-life when compared to clonidine, another commonly used alpha 2 adrenergic receptor agonist. A reduced incidence of patient delirium and agitation has been reported as compared to more traditional equivalent dosages of combined midazolam/fentanyl sedation and analgesia or with propofol sedation. Moreover, the respiratory depression associated with opioid use can be eliminated, resulting in shorter ICU stays and more rapid endotracheal extubations. Dexmedetomidine has no significant depression of minute ventilation or respiratory response to elevated $PaCO_2$ or decreased PaO_2. In fact, dexmedetomidine has been used as a successful bridge for patients who suffer emergence delirium from more conventional benzodiazepine/opioids or volatile agents. However, it has not been useful for treatment of acute agitated delirium (Chapter 37).

In theory, the basal continuous infusion prevents significant decreases in the serum level of opioid while patients sleep, so they can avoid awakening with severe pain. The use of a basal infusion, however, has been demonstrated to increase opioid use without improving overall patient satisfaction or VAPS score. Still, respiratory depression has only rarely been reported with reasonable doses of PCA, and ICU patients on positive-pressure ventilators are generally safe with continuous basal infusions. Respiratory depression has been reported following postoperative hemorrhage because of a reduction in the volume of distribution that resulted in relatively high opioid concentrations. One report of meperidine overdose was attributable to a "runaway" malfunction of the PCA pump. However, meperidine is not recommended for PCA because of the potential for accumulation of normeperidine, a central nervous system (CNS) excitatory metabolite with a long half-life (Chapter 17). Normeperidine toxicity is more likely in patients with renal dysfunction. If a basal infusion is used with PCA, it must be appreciated that sleep and coadministered sedatives (Chapter 4) are synergistic in their respiratory depressant effects.

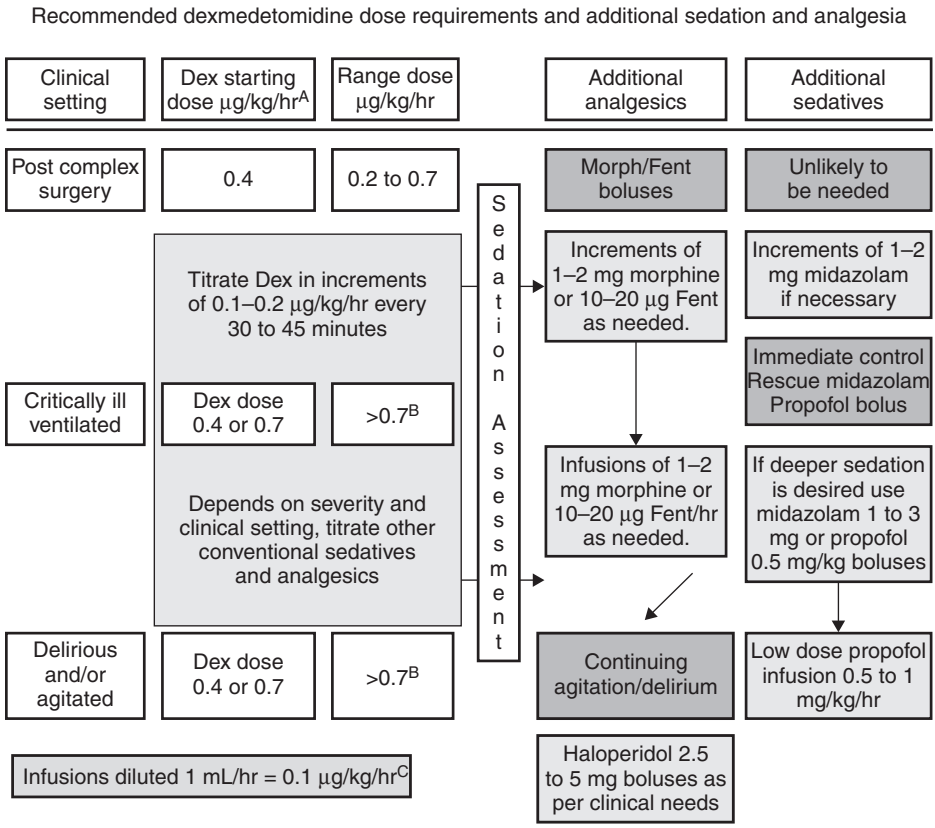


Figure 87.2 Schematic flow diagram of a protocol for dosing of dexmedetomidine with adjunctive agents for intensive care sedation. Dex, dexmedetomidine; Fent, fentanyl.

[A]Infusions should always start at 0.4 μg/kg/hr for one hour and be increased thereafter as required. Assessment of sedation and pain scales should be performed as part of ongoing evaluation at least every 4 hours.

[B]The maximum dose above 1 μg/kg/hr is not identified or approved. However, according to published literature, it is reasonable to use a dose up to 1.5 μg/kg/hr.

[C]This can be achieved by adjusting the volume of 5% DW or N/S added to 200 μg (full vials of dexmedetomidine) so that every milliliter contains 0.1 μg/kg of dexmedetomidine. This will also avoid discarding any dexmedetomidine, thereby avoiding any wastage.

(Adapted from Shehabi Y, Both JA, Ernest D et al: Clinical application: the use of dexmedetomidine in intensive care sedation. Crit Care Shock 13:40-50, 2010.)

Dexmedetomidine dosing is often initiated with the administration of an IV bolus dose, which is associated with a predictable bradycardia. If this is undesirable, dexmedetomidine may be administered as a continuous IV infusion without a loading dose, wherein the peak effect is achieved after 2 hours of continuous infusion. Other medications can be used to supplement the sedative or analgesic properties of dexmedetomidine, and a dosing paradigm is shown in (Figure 87.2). Stable hemodynamics are commonly maintained when this regimen is utilized. Dexmedetomidine may be relatively contraindicated in patients with free flap reconstructive surgery or after cerebrovascular interventions, as alpha 2 agonists may precipitate a local vasoconstriction (in denervated arteries). High-grade atrioventricular (AV) block has also been a reported side effect in patients and may require pacing.

INTERCOSTAL NERVE BLOCKS

Percutaneous intercostal nerve blocks with local anesthetics can be performed for patients with unilateral chest or abdominal wall somatic pain. This simple technique has been found to give superior analgesia compared with systemic opioids. A shortcoming of the technique, especially in the ICU setting, is the relatively brief duration of action of the block, requiring multiple intercostal nerve injections despite the use of a long-acting local anesthetic. These are time consuming and increase the risks of pneumothorax and intravascular injection. When local anesthetics are effective, continuous intercostal catheterization can be performed, obviating the need for repetitive injections.

CONTINUOUS NERVE BLOCKS

Some surgical procedures are amenable to the placement of catheters for delivering continuous or bolus infusions of local anesthetics to manage postoperative pain. This technique typically uses a fixed concentration of drug but allows for variable flow rates to increase/decrease coverage. Infusion of a local anesthetic for continuous nerve blocks can decrease postoperative opioid usage and improve pain score after a surgical procedure (e.g., thoracotomy).

NEURAXIAL ANALGESIA

Perispinal (subarachnoid or epidural) deposition of local anesthetics and opioids in combination or separately can provide effective postoperative analgesia. These two classes of analgesics act at differing sites along the nociceptive pathway, and they have differing profiles of side effects (Table 87.2). Local anesthetics and opioids are often combined to permit synergism with less untoward effects. It is preferable to place the catheter within the desired dermatomal area to be treated in an effort to minimize the volume of infusion required for analgesia (see Chapter 101, Figure 101.1, for dermatomal distributions).

Local Anesthetics in Neuraxial Analgesia

The earliest description of the placement of an epidural (caudal) catheter for postoperative pain management dates to 1949. The technique involved intermittent boluses of local anesthetic, which can cause unwanted effects like motor weakness and sensory and autonomic blockade. Thus, ICU patients with hypotension or hypovolemia are not good candidates for what, in effect, is a widely

TABLE 87.2 ■ **Comparative Profile of Local Anesthetics and Perispinal Opioids**

Characteristics	Local Anesthetics	Opioids
Site of action	Nerve roots	Dorsal horn
Inhibition	Global-axonal conduction	C and Aδ fibers*
Side Effects		
Cardiovascular	Hypotension, bradycardia	None
Central nervous system	None (unless overdosed)	Sedation, somnolence
Respiratory	None (unless overdosed)	Depressed respiration
Gastrointestinal	Nausea with hypotension	Central nervous system–mediated nausea
Genitourinary	Urinary retention	Urinary retention
Peripheral nervous system	Motor or sensory block, or both	Pruritus

*Spares motor, autonomic, and proprioceptive fibers.

As an example of the effectiveness of this approach, in their 1987 report, Yeager and colleagues compared outcomes of high-risk surgical patients randomly assigned to two groups. One group received general anesthesia and conventional prn systemic opioids. The other group received epidural anesthesia and postoperative epidural analgesia. The epidural group not only had significantly lower mortality and morbidity rates but also had significantly shorter ICU stays and reduced hospital costs.

distributed sympathectomy. Continuous slow infusions (3 to 8 mL/h) of a low concentration of local anesthetic (e.g., 0.05% to 0.15% bupivacaine) without any bolus administration prevent profound sympathetic blockade and permit time to counteract undesirable reductions in sympathetic tone. Potent analgesia can be achieved in many patients with a neuraxial local anesthetic alone. This is a time-tested regimen that can be especially useful for ICU patients who are hypertensive or could otherwise benefit from a reduction in blood pressure.

Perispinal Opioids

The first clinical use of epidural and subarachnoid opioids in humans occurred in 1979. Neuraxially administered opioids act by selective suppression of the activity of substantia gelatinosa nociceptors. Compared with local anesthetics, the use of opioids in this manner minimizes sensory motor and autonomic blockade and causes fewer physiologic cardiovascular changes (minimal changes in cardiac preload, output, or peripheral vascular resistance). In addition, a low toxicity reversal agent (naloxone) is available. Compared with systemic opioids, perispinal opioids show a reduction in side effects, such as somnolence, sedation, and ileus, and are not associated with spasm of the sphincter of Oddi or CNS or cardiovascular system excitability or toxicity. Perispinal administration of opioids markedly increases their potency and the duration of their analgesic effect.

PATIENT-CONTROLLED EPIDURAL ANALGESIA

Patient-controlled epidural analgesia (PCEA) combines the superior analgesic qualities of spinal local anesthetics or opioids and the increased patient satisfaction of PCA (Table 87.3). Studies have shown superior analgesia with significantly less sedation and anxiety with morphine administered by PCEA compared with IV PCA morphine. The rapid onset (3 to 5 minutes) of lipophilic opioids like fentanyl makes them the logical agent of choice for PCEA, using small doses with short lockout intervals. This lipophilic property, however, can also result in substantial systemic uptake. Because IV, subcutaneous, or epidural fentanyl provides similar analgesia with comparable serum levels at 18 and 24 hours, the specificity of neuraxial administration of lipophilic opioids, like fentanyl, has been questioned.

Side Effects of Patient-Controlled Epidural Analgesia

The following sections discuss various side effects of PCEA. Their management is summarized in Figure 87.3.

Nausea and Vomiting. Although opioids may stimulate the chemoreceptor trigger zone of the medulla, causing nausea and vomiting, these are common postoperative events even in the absence of opioid administration. Visceral traction, ileus, anticholinergic therapy, vagal innervation, increased intracranial pressure, and nasogastric (NG) tube displacement also contribute to postoperative nausea and emesis. Treatment may be prophylactic (NG tube suction and

TABLE 87.3 ■ **Recommendations for Patient-Controlled Epidural Analgesia (PCEA) Dosing**

Drug Concentration	Bolus (mL)	Lockout (min)	Basal Infusion (mL/h)
Morphine 0.01% with 0.05% bupivacaine	Abdominal: 5–7 Thoracic: 2–5	20–30	Abdominal: 4–10 Thoracic: 2–7
Fentanyl 0.0002% with 0.05% bupivacaine	Thoracic: 2–5	10–20	Thoracic: 2–5
Fentanyl 0.0005%	Thoracic: 2–7	10	Thoracic: 2–5

administration of ondansetron, metoclopramide, or droperidol) or responsive (naloxone, NG tube repositioning, prochlorperazine).

Pruritus. The mechanism of pruritus is unclear but may be related to opioid modulation of normal cutaneous afferent sensory integration at the spinal level. It is usually not seen for a period of 2 to 6 hours after administration. Diphenhydramine has been used as initial treatment even though the mechanism of pruritus does not involve histamine release. Naloxone may be administered intermittently (40 μg bolus IV) or by continuous low-dose infusion (40 to 100 μg/h) for refractory symptoms. Nalbuphine intermittent dosing (1 mg) or continuous dosing (2.5 mg/h) also provides satisfactory relief.

Urinary Retention. The true frequency of urinary retention following postoperative spinal opioid administration is masked by the common presence of a Foley catheter for the first 1 to 2 postoperative days, especially in the ICU patient population. Similar to nausea and vomiting, urinary retention is a common postoperative occurrence, whether or not spinal opioids have been used. Activation of spinal opioid receptors, however, is known to cause detrusor muscle relaxation, which, in turn, increases bladder capacity. These changes are reversed by naloxone, and bethanechol has also been reported to induce contractile responses. In addition to the use of neuraxial opioids and local anesthetics, intraoperative use of anticholinergic drugs may potentiate urinary retention. Many patients do not have detrusor dysfunction with epidural analgesia, depending on the level of the catheter, the composition and rate of the infusate, and patient sensitivity.

Somnolence. The use of potent anesthetic agents and adjunctive drugs is a common cause of somnolence in the postoperative period. Spinal opioid–induced somnolence is related to central

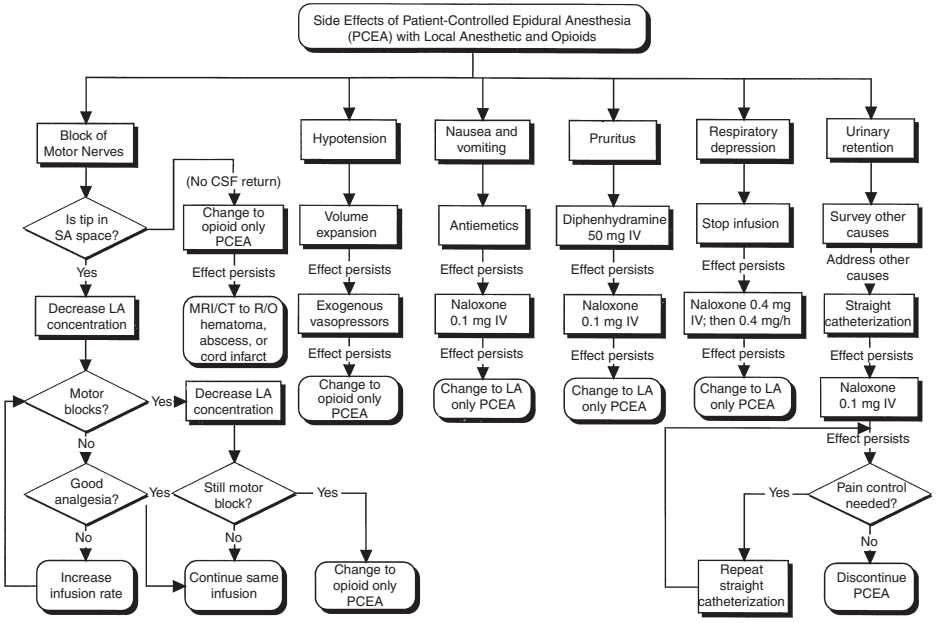


Figure 87.3 Schematic flow diagram illustrating the spectrum of side effects of patient-controlled epidural anesthesia (PCEA) and their management. SA, subarachnoid space; LA, local anesthetic; CSF, cerebrospinal fluid; MRI/CT, magnetic resonance imaging/computed tomography; R/O, rule out; IV, intravenously.

effects on the reticular activation system by rostral spread in the cerebrospinal fluid. Somnolence is a serious side effect of spinal opioids and must be treated to prevent respiratory depression. The possibility of hypercapnia from respiratory depression should be entertained in any somnolent ICU patient.

A four-point observer sedation score has been described to evaluate ICU patients receiving spinal opioids (Table 87.4). An observer sedation score of 2 warrants close observation, whereas a score of 3 warrants intervention. A score of 4 should never be reached. Somnolence is treated with oxygen therapy, cessation of continuously infused sedatives or opioids, and specific reversal agents (flumazenil, physostigmine, or naloxone) as appropriate.

Respiratory Depression. Intraspinal morphine administration has been associated with delayed onset of respiratory depression. This problem is related to the hydrophilic nature of the morphine sulfate molecule, which relegates it to remain primarily within the cerebrospinal fluid and be slowly transported to supraspinal centers. The more lipid-soluble drugs (fentanyl and sufentanil) may be associated with a lower incidence of hypoventilation, but they are limited in their duration of analgesia and spread within the neuraxis. Occurrence of respiratory depression following spinal morphine is rare: 1 in 1000 for mild cases (respiratory rate < 12/min) and 1 in 10,000 for severe cases (respiratory rate < 8/min). Risk factors for the development of this complication are related to patient, drug, and technique. Patients older than 60 years of age and patients with respiratory disease or severe debilitation are at higher risk. The use of hydrophilic opioids in large doses or in large volumes increases the risk of respiratory depression. Finally, the concomitant use of parenteral opioids and the use of thoracic (versus lumbar) epidural or subarachnoid administration also increase the risk of respiratory depression.

The potential for respiratory depression necessitates the immediate availability of oxygen and reversal agents (naloxone) at any site where patients are being so treated. Severe respiratory depression should be treated with an IV loading dose of 0.4 mg of naloxone followed by a continuous IV infusion at 0.4 mg/h.

Conclusion

Many patients now see adequate analgesia as a right rather than a privilege, and major improvements in pain management make that possible. With knowledge of the expected hemodynamic and CNS side effects of the many different analgesic regimens and with the input of specialist consultants in acute pain management, if needed, one can design a stable and effective regimen, even in the most critically ill patient. The psychologic trauma of unrelenting pain in a paralyzed and ventilated patient is unique to the operating room and the ICU. Failure to treat pain for fear of eliminating adrenergic stimulation is an archaic and inappropriate response. In this circumstance, one should give exogenous catecholamines and relieve the pain rather than rely on pain to augment vascular resistance. Moreover, the physiologic

TABLE 87.4 ■ **Sedation Score to Evaluate Patients Receiving Spinal Opioids**

Score	Clinical Manifestations
1	Alert, oriented, initiates conversation
2	Drowsy, oriented, conversant
3	Very drowsy, disoriented, but respondent
4	Stuporous to unarousable, disoriented, nonrespondent

From Nemethy M, Paroli L, Williams-Russo PG, Blanck TJJ: Assessing sedation with regional anesthesia: inter-rater agreement on a modified Wilson Sedation Scale. Anesth Analg 94:723-728, 2002.

effects of untreated pain can harm the cardiovascular and renal systems through tachycardia and decreased regional blood flow.

There is now no reason for ICU patients to suffer severe pain postoperatively. The increasing and appropriate expectations of patients and family compel adoption of effective analgesic regimens.

An annotated bibliography can be found at www.expertconsult.com.

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This important article documented decreased morbidity and costs with epidural analgesics.

CHAPTER 88

Cardiac Surgery

Bilal Shafi ■ Pavan Atluri ■ Benjamin A. Kohl

The field of cardiac surgery has seen remarkable advances. Procedures that once required a large sternotomy incision and institution of cardiopulmonary bypass are now being done through small incisions in the chest with the heart still beating. Similarly, many procedures that historically required long periods of aortic and visceral ischemia in order to replace segments of aorta with prosthetic grafts are now being approached percutaneously and treated by the deployment of stent devices, obviating the need for prolonged malperfusion. Indeed, many of these patients do not require intensive care unit (ICU) attention postoperatively. Concomitant with these advances, however, is an aging population with a greater number of comorbid conditions, many of whom have previously undergone myriad interventional or open surgical procedures prior to presentation. It is therefore not surprising that the perioperative care of the cardiac surgical patient has become more complex, requiring the intensivist to have a thorough understanding not only of physiology but of the technical aspects of the devices and procedures. Although a comprehensive review of cardiac surgery is beyond the scope of this book, this chapter reviews the basic tenets of these complex operations and provides a pathophysiologic foundation upon which to approach the management of these patients in the ICU.

Effects of Cardiopulmonary Bypass

Understanding the cardiopulmonary bypass (CPB) circuit and the associated complications allows more effective and thoughtful care of these patients postoperatively. The CPB machine diverts venous blood through a membrane oxygenator, where oxygen is added and carbon dioxide is removed, and then returns this blood (now oxygenated and ventilated) to the arterial system at a physiologic pressure such that the perfusion to key organs remains adequate. Although simple in concept, the reality is that initiating CPB and exposing a patient's entire cardiac output to foreign material, as well as converting organ perfusion from a state of pulsatile to continuous flow, create such enormous physiologic perturbations, at both at an organ and a cellular level, that the subsequent inflammatory cascade can be devastating if not managed appropriately in the perioperative period. Indeed, the majority of complications encountered after heart surgery can be attributed to the deleterious effects of CPB. To effectively manage the consequences of CPB, it is important to have a basic understanding of the bypass circuit, the potential complications that can arise while on CPB, and the ensuing inflammatory events that result from a patient's blood interacting with artificial surfaces.

The basic CPB circuit (Figure 88.1) is composed of a large venous catheter (inflow), a reservoir, a centrifugal or roller pump, an oxygenator, a heat exchanger, a debubbler, and an arterial catheter (outflow). Inflow of venous blood to the reservoir occurs primarily by gravity. Depending on the procedure, these venous catheters can be placed either centrally (e.g., right atrium, inferior vena cava, superior vena cava) or peripherally (e.g., femoral vein, internal jugular vein). Blood loss in the operative field is collected by pump suckers and also returned to the venous reservoir. Reservoir blood is then pumped through the oxygenator and heat exchanger. In turn, the warmed and oxygenated blood is infused into the arterial system via a cannula placed either centrally (e.g., ascending aorta, aortic arch) or peripherally (e.g., femoral or axillary artery).

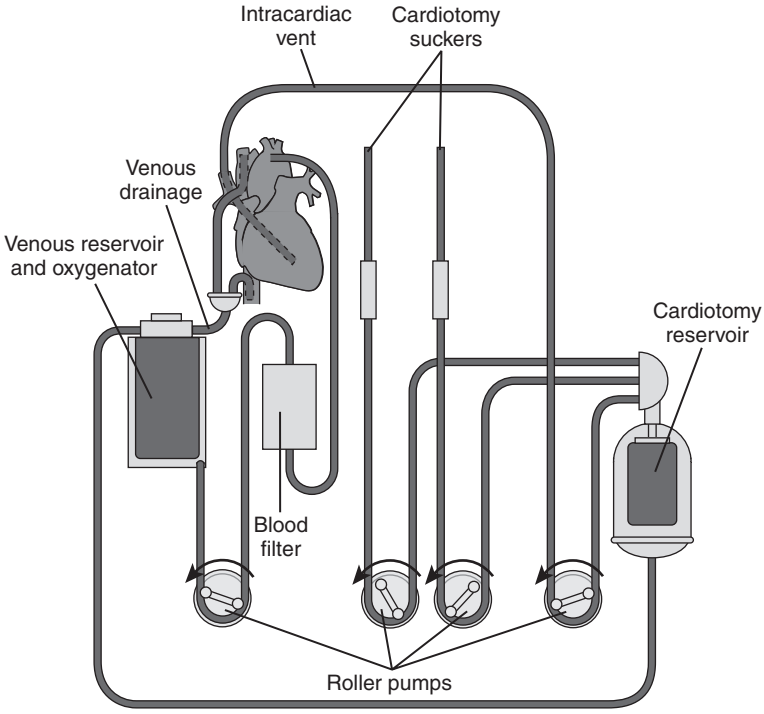


Figure 88.1 Cardiopulmonary bypass circuit. *(From Waldhausen JA, Pierce WS, Campbell DB: Surgery of the Chest, 6th ed. St. Louis: Mosby, 1996.)*

Essential to this entire process is the need for profound systemic anticoagulation to prevent thrombin formation in the pump. This is usually attained by the administration of large amounts of unfractionated heparin and can be followed by frequent measurements of activated clotting times (ACTs). Typically, heparin is administered prior to aortic or venous cannulation, and the ACT is verified to be > 350 to 400 seconds. Heparin titration protocols have been developed based on individual dose response curves to ensure the patient is not under- or overdosed with heparin.

Exposure of blood to the CPB circuit results in a massive systemic inflammatory response syndrome (SIRS), which, if left unchecked, ultimately manifests as end organ dysfunction in the early postoperative period. These complications are often magnified in patients who sustain prolonged bypass times, patients with preexisting organ dysfunction, or patients who sustain extremes in blood pressure during the operation.

Complement activation induced by exposure of plasma to the foreign CPB circuit causes a generalized inflammatory reaction characterized by the release of multiple cytokines, lymphokines, and proteases. Furthermore, this cascade of events augments platelet activation, coagulation, and fibrinolysis. The resulting coagulation contributes to ischemia-reperfusion injury in various end organs. *Platelet disruption* occurs as a result of direct contact with the circuit's inner surface, especially at the level of the oxygenator. Platelet dysfunction also occurs as a consequence of complement-induced opsonization in addition to the generalized inflammatory state. Ultimately, the *fibrinolytic pathway* is activated by CPB increasing levels of tissue plasminogen activator (tPA) in response to endothelial damage, platelet activation, and complement activation. Hemodilution and consumption of these clotting factors contribute to a bleeding diathesis postoperatively. *Red blood cell disruption*,

which manifests as hemoglobinuria, correlates directly with the intensity of pump sucker use as well as with the total duration of CPB. White blood cell activation and subsequent sequestration in the lungs can occur as a result of CPB. When combined with complement activation and high levels of circulating cytokines, this can lead to pulmonary edema and injury and, rarely, postoperative acute respiratory distress syndrome (ARDS).

Myocardial Protection

An essential component to most cardiac surgical procedures is ensuring viability of the heart while the aortic cross-clamp is in place (the period of cardiac ischemia). When CPB is first initiated, blood flow and oxygenation to the heart persist (via flow through coronary arteries). However, many operations on the heart require a bloodless field and cessation of the heart's contractions. In order to exclude the heart from the bypassed blood flow, a clamp is placed on the ascending aorta, proximal to the arterial blood outflow from CPB, inhibiting blood from perfusing the myocardium. Although this ischemic period is necessary, a number of methods aimed at reducing myocardial oxygen consumption, restoring a modest amount of blood flow to the heart, and ensuring the heart remains empty optimize the conditions during the myocardial ischemic period, making it easier to come off CPB after cardiac reperfusion.

Decreasing myocardial oxygen consumption minimizes the need to constantly supply blood flow to the heart. Delivery of a high potassium concentration solution (cardioplegia) into the aortic root, proximal to the aortic cross clamp, and subsequently into the coronary arteries (assuming the aortic valve is competent) will arrest the heart in diastole, immediately decreasing oxygen consumption by at least 90%. Another key aspect of myocardial protection is ensuring that the heart remains empty throughout the procedure and does not fill with blood, causing distention of the cavities and increased myocardial oxygen consumption. This is attained by placement of catheters ("vents"), which continuously divert any intracardiac blood back into the CPB circuit.

Finally, both myocardial and systemic hypothermia are induced intraoperatively to help minimize oxygen consumption of all organs. Typically, cardioplegia is delivered to the heart at 9.0° to 15.0° C and the body is cooled to 32.0° C during CPB. This is achieved by cooling the blood externally while it is in the CPB circuit.

Evaluation of Cardiac Function in the Intensive Care Unit

In general, all patients are routinely admitted to the ICU after heart surgery. Many of these patients arrive to the ICU intubated with invasive hemodynamic monitoring and are receiving a variety of vasoactive infusions. It is essential in the early postoperative period to monitor recovery of heart function and recovery from anesthesia, to accurately quantify bleeding from chest tubes, and to evaluate end organ function.

INVASIVE HEMODYNAMIC MONITORING

Various forms of invasive hemodynamic monitoring are used to guide postoperative recovery of heart function, fluid management, and overall management in the ICU setting (Chapter 7). Continuous blood pressure is monitored via a radial or femoral arterial catheter. Many patients also have a pulmonary arterial catheter (PAC) in place, which can be helpful in assessing both right and left heart function. Importantly, in patients with a PAC, great caution should be taken if a pulmonary artery wedge pressure (PAWP) is deemed necessary, as many of these patients have multiple factors, including pulmonary hypertension and an acquired bleeding diathesis, that put them at high risk for balloon-induced rupture of the pulmonary artery, a usually fatal complication.

CHEST RADIOGRAPHS

Chest radiographs are essential in any postoperative cardiac surgery patient. They provide information on the degree of lung expansion and the presence of undrained pleural fluid, pneumothorax, fluid overload, or frank pulmonary edema. A dramatic enlargement in cardiac silhouette should also raise the possibility of ongoing mediastinal bleeding and cardiac tamponade (Chapter 54). The proper location of all invasive catheters, tubes, and the tip of the endotracheal tube should be documented and verified by chest radiograph.

ELECTROCARDIOGRAMS

The 12-lead electrocardiogram (ECG) can provide valuable information in the postoperative period including the presence of ischemia, arrhythmia, or conduction disturbances. Such findings may prompt a variety of therapeutic maneuvers, including pacing via temporary wires, administering a coronary vasodilator, performing an emergency echocardiogram or cardiac catheterization, or returning the patient to the operating room. It is therefore imperative that a postoperative electrocardiogram be obtained promptly upon arrival in the ICU and followed up as clinically indicated.

ECHOCARDIOGRAMS

Transthoracic and transesophageal echocardiography are essential modalities that should be available to all cardiac surgical patients during the intraoperative period and in the ICU. Transthoracic echocardiography (TTE) has the advantage of being non-invasive, but its use is often limited postoperatively in these patients because of the lack of "acoustic windows." In these cases, a rapid and accurate evaluation of cardiac function can be obtained by a transesophageal echocardiogram (TEE) in the ICU setting. Critical data often include anatomic information about chamber sizes, valvular structures, the integrity of any repaired or replaced structures, the presence of intracardiac air or thrombus, and pericardial effusion. The examination can also provide physiologic information about residual valvular stenosis or regurgitation, regional or global wall motion abnormalities, degree of cardiac filling and diastolic function, estimates of chamber pressures, and presence of intracardiac shunts. The TEE results can then be correlated with invasive hemodynamic measurements to guide appropriate therapy.

When available, echocardiographic examinations should always be compared to prior examinations. Technological advancements have led to the development of much smaller probes, similar in size to a nasogastric tube, which can be left in the esophagus for longer periods of time and can be interpreted at the bedside by the intensivist.

WIRES AND DRAINS

Chest tubes are placed for most cardiac surgical procedures in the mediastinal or pleural space to drain any fluid and quantify postoperative bleeding. In addition to monitoring for bleeding, these tubes help prevent tamponade and lung hypoinflation because of a pneumothorax or pleural effusion. Accurate assessment of urine output by use of an indwelling Foley catheter is essential in these patients postoperatively, not only as a surrogate for renal function but as a measure of adequate cardiac output and to help manage fluid balance. Finally, most patients will have temporary epicardial atrial and ventricular wires placed at the conclusion of surgery. These wires can be used not only to pace the heart, but when included as a "lead" on an ECG, they can be useful for differentiating various arrhythmias.

Postoperative Complications

MYOCARDIAL STUNNING AND CARDIOGENIC SHOCK

As noted earlier, most cardiac surgical procedures require a period of cardiac ischemia during which time the heart is kept cold and mechanically quiescent by the use of cardioplegia and topical cooling. Despite the low temperature and diastolic arrest, cardiac metabolic demand continues, albeit at a low rate, such that cardiac demand for metabolic substrates may exceed the supply. This may manifest post-CPB by poor cardiac performance and often necessitate inotropic or mechanical support to help augment cardiac function in the early postoperative period. A comprehensive discussion on the assessment and management of cardiogenic shock can be found in Chapter 8.

If left ventricular failure persists despite maximal medical therapy, an intra-aortic balloon pump (IABP) can be inserted to increase diastolic coronary perfusion and further decrease afterload. Importantly, whereas balloon counterpulsation is often thought only as a support device for the left ventricle, it may be an essential component of therapy in patients with compromised coronary perfusion in order to augment right ventricular function. Other methods of pharmacologically assisting the right ventricle are with inotropes and agents that reduce pulmonary vascular resistance (e.g., inhaled nitric oxide or prostacyclin [epoprostenol]). Finally, as the right ventricular mass is much less than that of the left ventricle, its output has a greater dependency on rate. Thus, right ventricular failure often requires increased chronotropy (either with medications or via pacing). If, despite maximal therapy, right ventricular failure persists, a right ventricular assist device (RVAD) can be inserted. These devices facilitate drainage of blood proximal to the injured cavity (e.g., right atrium in the case of right ventricular failure) and mechanically pump the blood distal to the area of injury (e.g., pulmonary artery). Similarly, if the left ventricle is failing despite maximal therapy, a left ventricular assist device (LVAD) can be placed (removing blood from the left atrium and returning it to the aorta). When significant postoperative pulmonary dysfunction is present and adequate oxygenation cannot be attained by ventilatory maneuvers, extracorporeal membrane oxygenation (ECMO) can be used to maintain the patient on continuous CPB until adequate recovery occurs. In this circumstance, blood is drained from the right atrium or vena cava and passed through a membrane oxygenator before being returned to the systemic arterial system (akin to the intraoperative cardiopulmonary bypass circuit).

Despite all of these methods to augment cardiac function, there are times when the heart will fail to recover. Patients thus affected should be considered for heart transplantation and may require placement of a permanent or temporary assist device. Permanent LVADs currently approved by the U.S. Food and Drug Administration (FDA) include the Thoratec Heartmate II (Thoratec) and the Novocor (Baxter Healthcare Corporation). With technological and pharmacologic improvements, newer devices continue to be developed for use as a bridge to transplantation and for destination therapy. The most common complication associated with ventricular assist devices (VADs) is infection. If treated early, antibiotics alone can be successful. However, with delayed diagnosis and therapy, reoperation and placement of a new device may be necessary. These operations have a very high morbidity and mortality. Thus, if infection is suspected in these patients postoperatively, one should have a very low threshold to start broad-spectrum antibiotics and an infectious disease specialist should be consulted.

RESPIRATORY PROBLEMS

As a result of the surgical stress response and the inflammation induced by cardiopulmonary bypass, fluid accumulation and pulmonary edema are common in the early postoperative period. This may be compounded in a patient with preoperative congestive heart failure. As noted

earlier, the lungs are one of the major targets of the inflammatory activation caused by CPB. These adverse effects may cause postoperative ARDS requiring prolonged intubation and ventilation.

In addition, many patients with cardiovascular disease have risk factors for pulmonary disease, including advanced age and heavy past exposure to cigarette smoking. Chronic obstructive pulmonary disease is independently associated with numerous complications after cardiac surgery, including prolonged dependence on mechanical ventilation and postoperative pneumonia. In general, such patients should be managed intraoperatively and postoperatively in such a manner as to minimize the time on the ventilator and maximize pulmonary function. If the disease process does not allow an early extubation and the patient remains ventilator dependent, early tracheostomy should be considered to provide an easy and secure access for pulmonary toilet, simplify the weaning process, and enhance patient comfort compared with the continued use of an endotracheal tube.

BLEEDING PROBLEMS

Postoperatively, the cardiac surgical patient must be closely monitored for excessive bleeding and associated complications. Postoperative chest tube drainage must be monitored closely and, in general, an output > 500 mL in 1 hour or > 200 mL/h in 3 consecutive hours should warrant strong consideration for surgical reexploration. Similarly, an abrupt decrease in chest tube drainage with deterioration of cardiac function suggests the development of cardiac tamponade and often requires emergent reexploration. Mediastinal reexplorations carry a higher postoperative bleeding risk because of the need to dissect the scarred mediastinum.

Antifibrinolytic agents are commonly used intraoperatively and have been shown to reduce postoperative bleeding in many cardiac surgical operations. However, transfusion of blood or other blood products or both may be necessary to treat an ongoing coagulopathy. In such cases, transfusion should be data driven and based on measures of coagulation (prothrombin time [PT], partial thromboplastin time [PTT], platelet count, etc.). Some institutions use thromboelastography (TEG) to help guide their transfusion strategy.

NEUROLOGIC PROBLEMS

Cardiopulmonary bypass is associated with global neurologic impairment in a small but significant number of patients. Focal deficits can also occur and are usually due to embolic events from manipulation of the heart and vascular structures with embolization of atheromatous debris into the systemic circulation. Many patients with coronary artery disease also have significant arthrosclerotic disease involving the extracranial and intracranial cerebral circulation. Nonpulsatile flow at lower mean arterial pressure during CPB may cause ischemia to a region of brain distal to a vessel with critical stenosis.

When significant carotid artery disease is suspected, full preoperative carotid evaluation should be carried out when feasible. If the patient has clinical symptoms resulting from the carotid disease and has compensated cardiac disease, carotid endarterectomy should be performed first, followed by cardiac surgery. If the cardiac disease is poorly compensated, simultaneous carotid and cardiac surgery should be considered.

Although the factors that contribute to global neurologic dysfunction are not fully understood, embolization of particulate matter and microbubbles likely occur during CPB (despite the use of in-line filters) and play an important role in its pathogenesis. Furthermore, aortic atheromatous disease is often underestimated, and intraoperative embolization from aortic plaques can result during cannulation, aortic cross-clamping, or resumption of pulsatile flow after an open chamber procedure. In the postoperative period, embolic strokes are most commonly due to atrial

fibrillation, the presence of new significant ventricular dyskinesia (leading to a left ventricular thrombus), or a residual intracardiac shunt (allowing a paradoxical embolus). Patients with atrial fibrillation or a left ventricular aneurysm should undergo systemic anticoagulation to decrease the frequency of embolism.

RENAL PROBLEMS

Renal function can be affected by the complement activation and generalized inflammatory response to CPB. Nonpulsatile flow during CPB may be particularly deleterious in patients with poor preoperative renal function or severe renal vascular disease. Free hemoglobin, caused by red cell damage from CPB, is regarded as injurious to the renal tubules and can contribute to acute renal injury, especially when combined with acidemia. Hematuria alone is not necessarily a marker of renal dysfunction but it is most often associated with a prolonged period on CPB. Prolonged periods of low cardiac output combined with catecholamine administration postoperatively can also contribute to acute renal failure. Optimizing kidney function is of paramount importance to successfully manage the massive fluid shifts and electrolyte imbalances following CPB and to ensure adequate oxygenation and early extubation. If the renal dysfunction is severe enough, hemodialysis or hemofiltration (either intermittent or continuous) may be necessary in the postoperative period (Chapter 20).

HEPATIC DYSFUNCTION

Because of its role in metabolism and coagulation, liver dysfunction can profoundly affect the outcome of any cardiac operation. Although the causes of liver dysfunction in the cardiac surgical patient are myriad, frequently it is a direct result of cardiac dysfunction. With progressive left and right ventricular failure, low cardiac output and venous hypertension act synergistically to cause hepatic dysfunction. Cirrhosis predating a cardiac surgical procedure confers significantly increased morbidity and mortality to the operation. Patients with cirrhosis typically have increased cardiac output (because of arteriovenous shunting). When such a high cardiac output cannot be maintained during the perioperative period, liver function can acutely deteriorate and may result in hepatic encephalopathy, hepatorenal syndrome, variceal bleeding, and death.

GASTROINTESTINAL PROBLEMS

Pancreatitis and splanchnic ischemia have been described after prolonged CPB, typically when vasopressors are used to maintain arterial pressure during bypass. Most vasopressors shunt blood flow away from the pancreas and the gut, leading to variable degrees of pancreatitis and, if severe enough, may cause patchy necrosis of the bowel. The benefit of attaining a particular blood pressure with a peripheral vasoconstrictor must be carefully weighed against these devastating risks. Attempts to minimize and discontinue their use should be undertaken frequently in the ICU.

Patients requiring prolonged postoperative ventilatory support are at risk for stress ulcers and gastritis and, unless contraindicated, should receive appropriate stress ulcer prophylaxis (Chapter 12). Furthermore, early institution of nutritional therapy is essential to a timely recovery. Enteral feeding is preferable, but the parenteral route should be used if the patient is not able to be fed enterally or in patients who are severely malnourished (Chapters 15 and 16). If prolonged ventilator dependency is expected and aspiration risk is significant, placement of a gastrostomy or jejunostomy tube should be considered when the tracheostomy is performed.

Conclusion

Patients undergoing cardiac surgical procedures typically have multiple comorbid conditions and often have a variable degree of organ dysfunction preoperatively. With the additional insult of such a large procedure and the exposure to cardiopulmonary bypass, these patients must be monitored closely and managed efficiently in the ICU. Understanding the procedures performed and the risks associated with the various intraoperative time periods (e.g., bypass time, cross-clamp time) is essential to predicting organ failure. The intensivist should be familiar with the variety of devices used, both for diagnostic and therapeutic purposes, to best manage these patients. Concomitant with all of this is the need for frequent and open communication with the cardiac surgeon. These patients rely on a team of individuals for optimal outcome, and critical decisions should not be made in isolation.

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CHAPTER 89

Craniotomy

H. Isaac Chen ■ Kevin D. Judy

Injuries of the brain have been described since medical antiquity. Trephined skulls have been found that date back to 7000 to 3000 BCE. One of the earliest recordings of craniotomies was in the Hippocratic writings *De Capitis Vulneribus* (ca. 460 to 370 BCE), which discussed the evaluation and treatment of head injuries. Today, craniotomies are a routine procedure, and many patients requiring craniotomy are admitted to the intensive care unit (ICU) for diagnosis, initial management, and postoperative care.

Common Indications for Craniotomy

TUMORS

Patients with brain tumors can present with headache, neurologic deficits, and seizures. New-onset seizures should be investigated by brain computed tomography (CT) or magnetic resonance imaging (MRI). Supratentorial tumors typically cause motor or sensory changes or cranial nerve dysfunction. Patients with tumors located in or near the optic chiasm, temporal lobe, parietal lobe, and occipital lobe should have a comprehensive neuro-ophthalmologic examination to formally evaluate visual fields.

Hydrocephalus is a major complication of supratentorial tumors, which can lead to herniation and, if not treated in a timely fashion, may cause rapid, progressive physiologic decompensation and ultimately death. If a tumor is proximate to the sella or is located in the suprasellar region, it is imperative to perform a comprehensive evaluation of the patient's pituitary hormonal status, including serum levels of prolactin, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, adrenocorticotropic hormone, growth hormone, insulin-like growth factor-1, cortisol, and alpha subunit.

Tumors in the posterior fossa should be evaluated for evidence of cranial nerve dysfunction or brain stem compression. Hypertension, bradycardia, or an altered respiratory pattern (Cushing's triad) can indicate brain stem compression. More subtle signs of this complication include agitation or an altered level of consciousness.

Acoustic neuromas arising from the eighth cranial nerve can cause loss of hearing, and these patients should be evaluated with an audiogram.

HEMATOMAS

Hematomas are often associated with significant head trauma necessitating direct admission to the ICU. However, bleeding may result from minor head trauma in the elderly because of brain atrophy and subsequent traction on bridging veins in the subdural space. Intraparenchymal hematomas can arise from trauma or may occur spontaneously secondary to hypertension, amyloid angiopathy, or an underlying lesion. In general, subdural hematomas arise from venous injury, whereas epidural hematomas are arterial in nature. Because blood extravasates at a higher pressure from arteries compared to veins, epidural hematomas often progress more rapidly than subdural hematomas.

The classic presentation of epidural hematomas is a brief episode of unconsciousness from concussion, a subsequent lucid interval, followed by progressive mental status deterioration. In clinical practice, however, patients rarely present in this fashion. The overwhelming majority of subdural and epidural hematomas arise in the supratentorial space, although they can occur in the posterior fossa as well. Subdural hematomas often cause headaches, confusion, aphasia, hemiparesis, or seizures. Epidural hematomas commonly present with a decrease in level of consciousness. Chronic subdural hematomas occur most often in the elderly and can present in a variety of manners including a decrease in the level of consciousness, focal hemiparesis, severe headaches, or new-onset seizures.

Acute subdural hematomas usually require a craniotomy for clot evacuation. Patients with chronic subdural hematomas can be treated in an expectant fashion. Although most chronic subdural hematomas can be evacuated using burr hole drainage, those that are not fully liquefied or that are loculated may require a full craniotomy for evacuation. In the elderly, brain atrophy may prevent reexpansion of the brain following subdural evacuation, which can lead to recurrent hematomas.

Epidural hematomas usually expand more rapidly because of the arterial bleeding underlying the pathology and often need to be evacuated more expeditiously than subdural hematomas. A clot that causes mass effect, midline shift, or a significant neurologic deficit should be evacuated immediately. The indications for evacuation of intraparenchymal hematomas are unclear, as these surgeries have not been shown to improve neurologic deficits but only represent lifesaving procedures. The Surgical Trial in Intracerebral Haemorrhage (STICH), completed in 2005, compared a strategy of early surgical decompression (within 72 hours of presentation) with conservative medical management. In this large (n = 1033 representing 83 hospitals in 27 countries) randomized trial, there was no difference on early or 6-month mortality between the two groups. Although there were no overall benefits to early surgical intervention (primary outcome), there was a small benefit to surgical decompression noted in younger patients with hematomas that came within 1 cm of the cortical surface.

ANEURYSMS AND ARTERIOVENOUS MALFORMATIONS

Aneurysms typically present after rupture, causing subarachnoid hemorrhage and a headache that is often described as the "worst headache of my life." Arteriovenous malformations present most commonly with hemorrhage and seizures though they can also manifest as a focal neurologic deficit or coma. The causes of hemorrhage are myriad but they frequently occur during physical activity, bowel movements, or sexual intercourse.

Patients with subarachnoid hemorrhage present with varying levels of consciousness, ranging from fully alert to comatose. The Hunt and Hess classification is used to estimate the patient's clinical status and prognosis (Table 89.1).

TABLE 89.1 ■ **Hunt-Hess Classification of Subarachnoid Hemorrhage**

Grade	Description
0	Unruptured
1	Asymptomatic, mild headache
2	Moderate severe headache, cranial nerve findings
3	Focal neurologic deficit, lethargy, confusion
4	Stupor, hemiparesis
5	Coma, extensor posturing

Hunt and Hess grades 1 to 3 are considered low grade and these patients are considered to be good surgical candidates for aneurysm occlusion. Grades 4 and 5 are considered high grade and represent a poor prognosis, with a meaningful survival that is usually quoted to be less than 10%. These patients should be treated with endovascular occlusion.

Management is dictated by the initial neurologic deficit.

Intensive Care Evaluation and Management

NEUROCRITICAL CARE MONITORING

Key principles in neurocritical care, regardless of the pathology or procedure, include the prevention of secondary insults to the brain, ischemic or otherwise, and the maintenance of cerebral blood flow (CBF). Traditionally, these goals have been achieved through monitoring of intracranial pressure (ICP) and maintenance of an appropriate cerebral perfusion pressure (CPP) (Chapter 41). Intraparenchymal bolts for measuring ICP are inserted in patients with a neurologic exam that is difficult to follow, typically equivalent to a Glasgow Coma Scale of 8 or less. Cerebral perfusion pressure is calculated as the difference between mean arterial pressure (MAP) and ICP. Standard thresholds for intervention are an ICP greater than 20 mm Hg or a CPP less than 60 mm Hg, although care should be tailored on an individual basis.

Treatment of intracranial hypertension should be based on a stepwise algorithm starting with sedation (Chapter 5) and osmotic therapy (i.e., mannitol or hypertonic saline). Hyperventilation can be used acutely to lower ICP but is not useful for the long-term management of elevated ICP. If these strategies do not control intracranial hypertension, cerebrospinal fluid drainage via ventriculostomy placement and institution of pharmacologic paralysis (Chapter 6) may be necessary. Decompressive hemicraniectomy and pentobarbital coma are often reserved for intractable intracranial hypertension.

Other methods of monitoring cerebral physiology have been explored because of evidence that ICP- and CPP-based care sometimes fail to detect episodes of cerebral compromise. Brain oxygen electrodes are a useful adjunct for detecting brain hypoxia, and there are data to support improved clinical outcomes using this technology. In addition to their traditional role in seizure management, electroencephalography (EEG) can be utilized to detect ischemia using various algorithms. Cerebral microdialysis is a method for analyzing cellular metabolites in the brain. The lactate-pyruvate ratio is the most well-studied marker of cerebral metabolic dysfunction, but it, along with other microdialysis markers, is primarily a research tool currently and therefore is not routinely used in the clinical setting.

HEMATOMAS

Small subdural hematomas with no mass effect may be treated conservatively with observation and a repeat CT of the head in 24 hours (Table 89.2). If the patient experiences progressive neurologic deficit or the size of the clot increases with time, surgical intervention may be indicated.

SUBARACHNOID HEMORRHAGE

Patients presenting with aneurysmal subarachnoid hemorrhage (SAH) should be admitted to the ICU for close neurologic monitoring. In patients with concomitant hydrocephalus, a ventriculostomy should be placed, which often causes dramatic improvement in patients with poor Hunt and Hess grades. Patients with large hematomas require urgent operative decompression and aneurysm clipping. Prompt preoperative vascular imaging is desirable to define vascular anatomy and to determine the presence and location of intracerebral aneurysms. Conventional cerebral

TABLE 89.2 ■ **Evaluation of Various Types of Intracranial Pathology**

Suspected Pathology	Radiographic Study
Hematoma	Noncontrast computed tomography
Intracranial tumor	Magnetic resonance imaging with and without contrast
Aneurysm and arteriovenous malformation	Computed tomography to confirm subarachnoid hemorrhage and rule out hydrocephalus
	Cerebral angiogram to diagnose aneurysm, arteriovenous malformation
Vasospasm	Transcranial Doppler or cerebral angiogram

angiography remains the gold standard, but some consider CT angiograms an acceptable alternative as the initial study of choice. Subarachnoid hemorrhage can cause electrocardiographic abnormalities such as T-wave abnormalities, QT prolongation, ST segment changes, permanent U waves, and rhythm abnormalities. These electrocardiographic changes are reflective of subendocardial ischemia, hemorrhage, or focal areas of myocardial necrosis. A stress-induced cardiomyopathy (Takotsubo cardiomyopathy) has also been associated with subarachnoid hemorrhage.

The ideal timing of surgery for intracranial aneurysms has evolved. The current consensus is that aneurysm occlusion, either by surgery or endovascular coiling, should not be delayed. Following aneurysm surgery, an intraoperative or postprocedure angiogram should be performed to document aneurysm occlusion and to ensure that the aneurysm clip has not inadvertently compromised any vessels.

If hypothermia was induced during surgery for purposes of cerebral protection, patients should be rewarmed before a postoperative neurologic evaluation is performed. The discovery of a new focal neurologic deficit mandates performance of a head CT. If the CT scan is normal, the patient should undergo angiography to assess for the presence of vasospasm before mental status changes are attributed to metabolic etiologies or delirium.

The risk of rebleeding is 4% within the first 24 hours and then 1.5%/day for the following 2 weeks after aneurysm rupture. Hydrocephalus, causing a decreased level of consciousness, can occur up to 2 weeks after the subarachnoid hemorrhage. The window for vasospasm is usually 3 to 14 days after aneurysm rupture.

VASOSPASM

Clinical Manifestations and Diagnosis

Vasospasm is a poorly understood complication of subarachnoid hemorrhage that can lead to cerebral infarction or death. Clinically relevant vasospasm occurs in 20% to 30% of subarachnoid hemorrhage patients. With the onset of a delayed focal neurologic deficit or a newly depressed level of consciousness, a noncontrast head CT scan should be obtained to rule out hydrocephalus or a new hemorrhage. In the absence of these entities, the diagnosis of vasospasm is suspected.

The early diagnosis of vasospasm is imperative to prevent permanent neurologic morbidity and death. Thus, vasospasm screening tools are routinely used in the ICU. Transcranial Doppler offers a non-invasive method of recording blood flow velocities in the proximal cerebral vasculature. High-velocity blood flow (> 120 cm/sec) and significant increases in blood flow velocity (> 50 cm/sec) suggest vasospasm. Electroencephalography algorithms can also assist in vasospasm detection by demonstrating areas of focal slowing indicative of ischemia. Perfusion deficits can be further investigated using CT or MRI studies. Computed tomography angiograms or conventional cerebral angiograms demonstrate narrowing or complete occlusion of involved arterial vessels.

BOX 89.1 ■ Treatment of Vasospasm after Subarachnoid Hemorrhage

Intravenous vasopressors (systolic blood pressure of 160–200 mm Hg)
Euvolemia (central venous pressure of 4–6 mm Hg)
Nimodipine (60 mg q4h orally or by nasogastric tube)
Statin
Endovascular intervention (angioplasty versus intra-arterial nicardipine)

Treatment

Therapy for vasospasm has evolved and involves optimization of volume status and blood pressure, administration of pharmacologic agents that have been shown to improve outcome, and endovascular techniques (Box 89.1). The historical practice of hypertension, hypervolemia, and hemodilution, known as "triple H" therapy, has been modified to include only hypertension and euvolemia. A central venous pressure of 4 to 6 mm Hg is targeted, using a combination of crystalloid and colloid infusion and fludrocortisone acetate, if necessary, to attain this goal. Vasopressors are used to increase the systolic blood pressure to a level that resolves neurologic deficits, which usually falls in the range of 160 to 200 mm Hg. Many patients demonstrate perfusion dependence, requiring the maintenance of a blood pressure below which a profound neurologic deficit develops. These therapies may induce congestive heart failure, and the placement of a pulmonary artery catheter may be indicated in certain patients.

Nimodipine is a calcium channel blocker that was initially thought to directly treat vasospasm. Studies did not bear out this hypothesis but did demonstrate improved outcomes in patients with subarachnoid hemorrhage. Statins have also been shown to improve outcomes in subarachnoid hemorrhage patients. The mechanism of this effect is not clear but may be associated with the anti-inflammatory properties of this class of drugs.

Endovascular techniques are the definitive intervention for vasospasm. Balloon angioplasty of the offending vessel is the most durable treatment. However, it cannot be applied within the region of an aneurysm clip because it may dislodge the clip and potentially damage or rupture the vessel. Alternatively, agents such as nicardipine can be directly injected into affected vessels. The benefits of intra-arterial injections are more transient compared to angioplasty. If vasospasm persists, these therapies can be repeated.

GENERAL POSTCRANIOTOMY CARE

The neurologic examination is the ideal way to evaluate brain function. Headaches, especially if they are out of proportion to routine postoperative pain, should raise concerns for a postoperative hematoma. Changes in a patient's pupillary exam should be evaluated promptly with a full neurologic exam and brain imaging. Agitation and hypertension are consistent with posterior fossa herniation syndrome after posterior fossa surgery but may be incorrectly attributed to postoperative pain and treated with opioids. Patients with these symptoms should be promptly evaluated with CT.

In contrast, supratentorial herniation syndromes typically progress more slowly and manifest as lethargy, contralateral hemiparesis, a dilated pupil, and respiratory compromise. Thus, patients with these symptoms after supratentorial craniotomy should be investigated with CT before treatment with opioids. The brain has no pain receptors, and the only sources of pain from a craniotomy are the dura, scalp, and underlying facial muscles, which can be adequately treated with acetaminophen and low-dose opioids.

Patients who have had posterior fossa surgery are at risk for injury to cranial nerves IX, X, and XII, which innervate the pharynx and tongue. These patients are consequently at risk for airway compromise and should be observed closely after extubation. If there is concern regarding

the function of the lower cranial nerves, the patient should remain intubated until pharyngeal function is fully evaluated. When pharyngeal dysfunction persists, a tracheostomy should be performed for airway protection and clearance.

Coagulation profile and platelet count should be followed closely after intracranial hemorrhage and corrected when necessary to prevent further bleeding. Postoperative head CT is performed routinely within 24 hours to look for any other evidence of bleeding within the brain. After evacuation of an acute subdural or epidural hematoma, it is not uncommon for the underlying contused brain to swell, causing significant mass effect. Contusions that develop after evacuation of an epidural or subdural hematoma may require reexploration and reevacuation.

Although steroids have not been shown to be beneficial in treating cerebral edema after traumatic brain injury, they are very effective in patients following tumor surgery to combat brain swelling. The time period over which steroids are tapered depends on the malignancy of the tumor, the presence of any residual tumor, and the amount of edema on postoperative radiography. Nonsedating antiemetics such as ondansetron are acceptable for use in neurosurgical patients. Subcutaneous heparin for deep venous thrombosis prophylaxis is reasonable in the setting of stable intracranial hemorrhages and on the first postoperative day of uncomplicated craniotomies for tumors and vascular malformations.

Antifibrinolytic agents, such as aminocaproic acid (once used to reduce the incidence of rebleeding), have been shown to cause persistence of blood clot within the subarachnoid space. Because they may increase the incidence of vasospasm, their use has fallen out of favor.

All postcraniotomy patients should have their head elevated to at least 30 degrees to reduce venous engorgement of the brain. The patient undergoing an uncomplicated craniotomy for tumor may resume oral intake the evening of surgery or on the next day. Patients are encouraged to get out of bed the morning after surgery. In most cases, the patient can be safely transferred out of the ICU the day after surgery. Early ambulation is essential to prevent deep venous thrombosis and subsequent pulmonary emboli.

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CHAPTER 90

Major Abdominal Surgery: Postoperative Considerations

Nabil Tariq ■ Daniel N. Holena ■ Benjamin Braslow ■ Benjamin A. Kohl

Intensivists frequently care for patients undergoing major abdominal surgery for intra-abdominal malignancy, obstruction, or infection. As the population continues to age, an increasing proportion of postsurgical patients will be elderly and will likely have a multitude of comorbidities including atherosclerotic cardiovascular disease, chronic obstructive airway disease (COPD), and diabetes mellitus. Exacerbation of these chronic conditions resulting from the stress of critical illness and surgery should be expected, and a detailed understanding of the operative procedure is necessary in order to provide optimal postoperative care.

Operative Procedures (Table 90.1)

PANCREATIC RESECTIONS

Malignancy is the most frequent indication for pancreatic resection. When the malignancy is located in the head of the pancreas, a pancreaticoduodenectomy (Whipple procedure) is typically performed, which involves an en bloc resection of the pancreatic head and entire duodenum. Four anastomoses (gastroenteric, bilioenteric, enteroenteric, and pancreaticoenteric) are required to reestablish gastrointestinal (GI) tract continuity. The degree of physiologic perturbation secondary to an uncomplicated pancreaticoduodenectomy is moderate, primarily involving fluid shifts between intra- and extravascular compartments. Self-suctioning Jackson-Pratt (JP) drains are usually placed adjacent to the pancreatic and biliary anastomoses allowing rapid identification of an anastomotic leak. Stents may be placed through the anastomoses to promote patency. Major complications are often related to the integrity of the anastomoses and usually occur between 5 and 10 days postoperatively. It is important that the intensivist know the specific location of each drain or tube, all of which should be illustrated in the patient's record.

Mortality rates in centers performing more than 18 to 24 cases per year are less than 5% as compared to 10% to 15% for centers with < 5 cases per year.

Distal pancreatectomy for tumors in the tail of the pancreas does not typically require a pancreaticoenteric anastomosis as exocrine secretions continue to empty antegrade into the duodenum. Because the vasculature of the spleen is intimately associated with the tail of the pancreas, the spleen and distal pancreas are most often removed en bloc. Endocrine insufficiency is uncommon with the Whipple procedure or distal pancreatectomy. However, patients who undergo total pancreatectomy will immediately become diabetic. These patients also require pancreatic exocrine supplementation to aid food digestion once enteral nutrition is started.

Additional online-only material indicated by icon.

Postoperative bleeding occurs in 5% to 7% of patients and is the most frequent complication that necessitates an immediate return to the operating room. Although bleeding is frequently considered to be an immediate postoperative complication only, in reality about half of major bleeding episodes occur after the first day. These late bleeds may be associated with a pseudoaneurysm and consideration should be given to assessing and managing those using angiographic techniques.

TABLE 90.1 ■ **Major Abdominal Surgery and Its Common Complications**

Procedure	Complications
Whipple procedure	Third space losses into retroperitoneum; if total pancreatectomy is performed, diabetes and hyperglycemia; anastomotic breakdowns typically occur on postoperative days 5–10.
Hepatic lobectomy (> 50% of liver resected)	Jaundice is common, peaks on postoperative days 3–4; investigation warranted if persists beyond postoperative day 10. Hypoglycemia also common; patients may need 10% dextrose postoperatively; hepatic failure may occur in cirrhotic patients.
Esophagogastrectomy	Complications occur in 10%–25% of cases. Pulmonary complications frequent, often due to gastric aspiration. Anastomotic leaks in chest cause mediastinitis, empyema, or both.
Intestinal and reoperative surgery	Preoperative severe dehydration, contraction alkalosis, hypokalemia, and marked third space losses into obstructed bowel; continued third space losses occur postoperatively as well; intra-abdominal infection or fistula formation caused by inadvertent enterotomies or anastomotic leaks.

HEPATIC LOBECTOMY

Resection of 50% or more of hepatic parenchyma may result in hyperbilirubinemia, jaundice, hypoglycemia, hypoalbuminemia, hypophosphatemia, and hypokalemia. Jaundice and hypoglycemia are the most common sequelae of large hepatic resections. Jaundice usually peaks between 3 and 4 days postoperatively and should be investigated if it persists beyond 10 days. Hypoglycemia is often severe enough to warrant intravenous infusion of 10% dextrose. Liver regeneration involves rapid cell division as early as 24 to 72 hours after resection. This is an adenosine triphosphate (ATP)–dependent process that often results in severe hypophosphatemia and may cause reversible cardiac dysfunction, hypoventilation, or impaired immunity. Monitoring and aggressive repletion of serum phosphate levels are necessary to prevent such complications. The most serious complication of major liver resections, however, is fulminant hepatic failure—that is, hepatic metabolic and synthetic failure. This occurs more frequently in patients with underlying primary liver disease (e.g., cirrhosis) or those who have been exposed to hepatotoxic drugs. Drug metabolism, anesthetic clearance, and the production of clotting factors II, VII, IX, and X will be significantly altered after large hepatic resections. Large infusions of plasma are often required to prevent bleeding complications early on. Although hepatic clearance of lactate may be impaired in these patients, persistently elevated lactate levels in the posthepatectomy patient should be considered indicative of hypoperfusion until proven otherwise.

ESOPHAGOGASTRECTOMY

There are three principal open surgical approaches to esophageal resection and the postoperative course and associated complications differ depending on which technique is employed. Common to all of the procedures is an upper midline laparotomy incision through which the distal esophagus and proximal stomach are mobilized. After resection of the diseased portion of the esophagus, GI continuity is restored by anastomosing the tubularized stomach to the proximal esophagus. This anastomosis may be accomplished either through a thoracotomy or a left cervical incision depending on the extent of the resection. In general, complications following esophageal resection are more common than in other abdominal or thoracic operations, occurring in 10% to 25% of cases. Pulmonary complications may be related to the incisional pain from the thoracotomy or to loss of the lower esophageal sphincter, which predisposes the patient to aspiration of

gastric contents. Many patients with esophageal carcinoma present initially with malnutrition and chronic obstructive airway disease as comorbid conditions that complicate the postoperative care. Pleural effusions are common after these procedures and occasionally require chest tube placement to maximize lung inflation. The most feared surgical complication after esophagectomy is an anastomotic leak, which occurs more commonly in cervical anastomoses than thoracic anastomoses. Whereas a leak occurring from a cervical anastomosis is usually well tolerated and easily managed, leakage from intrathoracic esophageal anastomoses often leads to mediastinitis and is associated with a higher mortality rate. Frequent assessment of the drains and wound is imperative to help identify early signs of anastomotic failure. Persistent tachycardia is a sensitive, though not specific, indicator of anastomotic leak. A change in the quality or quantity of drain effluent or the development of wound cellulitis can be an early harbinger of a leak.

INTESTINAL AND REOPERATIVE ABDOMINAL SURGERY

Because reoperative abdominal surgery is frequently performed to treat intestinal obstruction, these topics are presented together. Physiologic derangements, such as severe dehydration, contraction alkalosis, hypokalemia, and intravascular fluid redistribution, frequently accompany intestinal obstruction. Reasonable preoperative attempts to correct these abnormalities are warranted to avoid substantial postoperative problems. Reoperative abdominal surgery may be prolonged and may involve significant blood loss. It is not uncommon for an extensive lysis of adhesions to take between 4 and 8 hours and for the bowel to be drained of several liters of luminal fluid. Postoperative intra-abdominal infection or fistula formation may occur because of iatrogenic enterotomies or anastomotic leaks. In general, the morbidity following surgery for intestinal obstruction approaches 25% to 30%. Advanced age, delay in operative intervention, and other comorbid conditions have been shown to be associated with increased complication rates. Malignant obstruction and obstruction caused by radiation enteritis also result in higher morbidity and mortality rates. Massive small bowel resection may be required if a large portion of the intestine has been infarcted. If this is necessary, short-gut syndrome (usually defined as less than 100 cm of remaining small bowel in the presence of a competent ileocecal valve) may result.

Postoperative Management

FLUID MANAGEMENT

Fluid losses during abdominal surgery are proportional to the extent of surgical dissection, length of operation, blood or extravascular fluid lost during surgery, and presence or absence of infection or fever. Although formulas exist that attempt to define "ideal" maintenance fluids for patients undergoing major abdominal surgery, they are based on an estimation of the degree of evaporative or insensible losses associated with laparotomy. For a standard midline incision, this is usually estimated to be 1 liter per hour while the abdomen is open. This is only an approximation, however, and is not a substitute for fluid management guided by urine output, estimated blood loss, acid-base status, hemodynamic data, and clinical assessment of perfusion (Chapter 86).

Postoperative fluid management is best approached by considering maintenance fluids separate from all other fluid requirements. Early in the postoperative course, patients require a maintenance IV fluid rate that is generally 1 to 2 mL/kg/h. These fluids should be isotonic crystalloids unless salt restriction is indicated such as in cirrhotic patients. Controversy exists as to whether maintenance fluids in the immediate postop period ought to contain dextrose. Supplemental fluids, including those required to replace measured and insensible losses, should be administered as needed in response to measured physiologic abnormalities such as hypotension, oliguria, low cardiac filling pressures, and so on. The choice of crystalloid or colloid depends on the resuscitative

Abdominal compartment syndrome (ACS) may occur in the postoperative setting when the abdominal fascia is closed but the viscera continue to swell secondary to ongoing resuscitation and inflammation. In such cases, reopening of the incision is often necessary with eventual closure days to weeks later.

Like other patients undergoing major surgery, patients undergoing major abdominal surgery sustain a stress or inflammatory response that causes fluid redistribution from the intravascular to the extravascular fluid compartment (the so-called third space) (Chapter 86). The presence of peritonitis may add dramatically to fluid loss into the peritoneum both intraoperatively and postoperatively.

Glomerular filtration rate decreases as the intravascular volume declines. This effective hypovolemia along with elevated levels of circulating catecholamines, aldosterone, and antidiuretic hormone (seen in the surgical stress response) enhances tubular resorption of Na^+ and water in an effort to maintain intravascular volume.

philosophy of the intensivist. Too aggressive of a volume resuscitation may contribute to or cause profound tissue edema. As this edema progresses in various organs it can cause decreased bowel motility, pulmonary congestion, impaired wound healing, and decreased mobility from limb edema. A large randomized, prospective trial in a heterogeneous ICU population demonstrated no difference in 28-day outcomes between patients resuscitated with crystalloid versus colloid.

PAIN CONTROL

Appropriate and effective pain management can help prevent postoperative pulmonary complications and decrease demands on the cardiovascular system. Historically, parenteral opioids have been the mainstay in providing postoperative pain relief (Chapter 87). Patient-controlled analgesia delivered parenterally or locally via subcutaneously placed catheters has been shown to be more effective than intermittent opioid dosing by care providers. Caution must be exercised when continuous or basal rate patient-controlled opioids are used, however, as the incidence of respiratory depression is higher than with intermittent dosing alone.

Neuraxial analgesia has emerged as the preferred method of pain control for patients undergoing major abdominal operations (Chapter 87). This method allows delivery of opioid, local anesthetic, or both directly to receptors surrounding the spinal cord. Because much lower serum concentrations of opioid result, less respiratory and central nervous system depression is observed. Active participation by patients in their own respiratory care—for example, performing deep breathing exercises with an incentive spirometer and coughing—is crucial in the postoperative period. Patients with epidural analgesia have been shown to more easily and effectively participate in these postoperative respiratory maneuvers and, as a result, can be mobilized earlier. Complications of epidural analgesia are rare and include infection, bleeding into the epidural space, postspinal headaches, and hypotension (Figure 87.2).

Nonsteroidal anti-inflammatory drugs are also useful in postoperative pain management because they have no respiratory or central nervous system depression. Some can be administered parenterally (ketorolac or ibuprofen) in patients who are receiving nothing by mouth.

Management of Tubes, Drains, and Stomas

Drainage Considerations. The performance of abdominal surgery often necessitates the placement of drains or tubes in various positions within the digestive tract, biliary/pancreatic ducts, or peritoneal cavity. Stomas, which are openings of the digestive tract onto the abdominal wall, may also be required. It is less important for the intensivist to understand the precise indications and technical features of these drainage and diverting methods than to have an appreciation of their practical management and the ability to assess the quantity and quality of effluent.

Two basic modalities of drainage are employed: passive and active. A passive drain relies on capillary action to remove fluid, whereas an active drain usually employs suction. Drains may be open or closed depending on whether or not the cavity they are draining is exposed to the atmosphere. A closed system is *theoretically* sterile as there is no direct communication with the environment. Most surgeons employ active closed drainage systems to drain blood, bile, pancreatic juice, or infected material from an abscess cavity.

Nasogastric Tubes. NG tubes deserve special mention because they are used so commonly. Despite this fact, a number of studies demonstrate that the routine use of an NG tube following abdominal surgery is not indicated. In a Cochrane review of 33 studies with more than 5000 patients randomized to routine versus as needed NG tubes, routine NG tube placement was associated with a delayed return of bowel function and increased pulmonary complications. Additionally, there was no increase in anastomotic complications in patients with as needed NG tubes. Nonetheless, advocates of their use believe that vomiting and aspiration, as well as suture line or abdominal wound disruption, may occur more frequently when they are not routinely placed.

Measured losses include blood or ascites from drains and GI contents from nasogastric (NG), intestinal, or pancreaticobiliary tubes and stomas. Unmeasured losses include ongoing third space losses and evaporative losses resulting from fever and open wounds. Use of abdominal vacuum dressings in patients whose abdomens have been left open allow accurate measurement of abdominal fluid. Because a precise determination of insensible loss may be difficult, monitoring surrogates of end-organ perfusion (e.g., urine output) and acid-base status plus hemodynamic monitoring are recommended to guide fluid replacement therapy accurately (Chapter 86, Figure 86.3 and Tables 86.3 and 86.4).

As a rule, one should assume that the operating surgeon has a clear purpose for any drainage tube. As a result, no such device should be removed or manipulated without prior discussion with the operating surgeon. Likewise, if a drainage tube becomes displaced or dysfunctional, the surgical team should be immediately notified. In most institutions, it is the responsibility of the surgical team to ensure that drains or tubes are carefully secured (usually by sutures) to the patient's skin and kept patent by intermittent stripping or flushing of the tubing.

Normal functioning of an NG tube requires patency of the associated sump port lumen, often colored blue in contrast to the main drainage port, which is usually clear. The sump port allows for atmospheric air to be pulled into the gastric lumen and prevent complete collapse of the gastric mucosa around the main tube openings when the stomach is empty. Water in the sump lumen can create an air lock and prevent flow, and therefore this port should only be flushed with air. A well-functioning NG tube should make a continuous gurgling sound, and there should be continuous movement of fluid material in the suction tubing as atmospheric air circulates through.

Removal of NG tubes usually follows evidence of return of bowel function, normally 3 to 5 days after surgery. Occasionally, high NG outputs in excess of 1 L/day persist beyond 3 to 5 days. When such output persists, an abdominal radiograph should be obtained to look for evidence of bowel obstruction or ileus as well as to confirm that the tip of the NG tube has not migrated into the duodenum, which could account for the large volume bilious output. It may be useful to remove the tube from suction for several hours followed by a check of residual gastric contents ("clamping trial"). If "residuals" (fluid that remains in the stomach after a certain time) are less than 150 to 200 mL/4 h, one can assume antegrade passage of gastric contents and consider removing the NG tube.

Intestinal Stomas. Intestinal stomas are created to divert the intestinal stream. They may be permanent or temporary and consist of either a free end of bowel or a side hole in a loop of intestine anastomosed to the abdominal wall. The primary acute complications associated with intestinal stomas are bleeding, necrosis, and separation from the abdominal wall. Bleeding can usually be controlled locally with a suture or by applying chemical cautery with silver nitrate sticks. Ischemia and necrosis are diagnosed by visual inspection of the stoma, which will appear purple or black when present. It is important to distinguish between a completely necrotic stoma and one in which the mucosa only has become necrotic. A useful technique to assess for this condition is to insert a test tube into the opening and, with a penlight, examine the more proximal mucosa for viability (it should appear pink or red). Ileostomies or proximal small bowel stomas can cause skin excoriation because their effluent is rich in bicarbonate and therefore quite alkaline. Colostomy output is usually less voluminous, of thicker consistency, and less likely to cause skin excoriation.

Another important aspect in the perioperative period is the potential for significant fluid and electrolyte losses from the GI tract through drainage or stomas. Table 90.2 shows the electrolyte content of gastrointestinal fluid losses to help in appropriate replacement.

NUTRITION

A comprehensive discussion of surgical nutrition is beyond the scope of this chapter (Chapter 15), but several points are particularly germane to the intensivist caring for postoperative abdominal surgery patients. Many patients undergoing abdominal surgery are elderly and have malignancies. These patients often have depletion of baseline visceral protein stores and a concomitant impairment in immunologic competence. These patients are at high risk for postoperative complications and have been shown to have increased mortality rates when compared with patients whose nutritional status is adequate. Early, aggressive nutritional support is therefore important.

Enteral nutrition is preferred over parenteral nutrition. If full enteral nutrition cannot be delivered, even low levels of enteral feeding (which do not meet full protein and caloric needs—so-called trophic feeds) may be helpful in preserving the gut-mucosal barrier function and maintaining immunologic function. Daily nitrogen and carbohydrate requirements can be met by administration of parenteral nutrition in these patients. Enteral nutrition can be provided by nasoenteric tubes placed beyond the pylorus or via a nasogastric (NG) tube in the stomach. An NG tube is preferable to smaller-diameter feeding tubes for gastric feeds because residuals can be checked more easily. Surgically placed feeding tubes that are distal to the ligament of Treitz

TABLE 90.2 ■ **Typical Electrolyte Content and Volume of Gastrointestinal Fluid**

	Sodium MEQ/L, mean (range)	Potassium MEQ/L, mean (range)	Chloride MEQ/L, mean (range)	Bicarbonate MEQ/L, mean (range)	Volume MEQ/L, range
Gastric juice, high in acid	20 (20–30)	10 (5–40)	120 (80–150)	0	1000–5000
Gastric juice, low in acid	80 (70–140)	15 (5–40)	90 (40–120)	5–25	1000–2500
Pancreatic juice	140 (115–180)	5 (3–8)	75 (55–95)	80 (60–110)	500–1000
Bile	148 (130–160)	5 (3–12)	100 (90–120)	35 (30–40)	300–1000
Small bowel drainage	110 (80–150)	5 (2–8)	105 (60–125)	30 (20–40)	1000–3000
Distal ileum and cecum drainage	80 (40–135)	8 (5–30)	45 (20–90)	30 (20–40)	1000–3000
Diarrhea stools	120 (20–160)	25 (10–40)	90 (30–120)	45 (30–50)	500–10,000

may have a lower incidence of aspiration in populations at high risk for this problem, but they are associated with other complications.

Postoperative patients generally have caloric requirements in the range of 25 to 40 Kcal/kg/day and protein requirements between 1.5 and 2.5 g/kg/day. Burn patients and patients with open abdomens or large granulating wounds usually have some of the highest protein requirements. It is important to remember that abdominal vacuum dressing effluent is quite rich in protein content, containing roughly 2 gm of nitrogen per liter of effluent (Chapter 15).

Postoperative Complications

PULMONARY COMPLICATIONS

The most common complications of upper abdominal surgery are pulmonary and occur in up to 50% of cases. Patients at high risk for such complications are smokers or those with preoperative dyspnea on exertion, cough, or copious sputum production. The precise role of preoperative pulmonary function studies prior to abdominal surgery is unclear, but patients with a maximal voluntary ventilation of less than 50% of predicted values have been shown to have significantly more pulmonary complications than those with a normal maximal voluntary ventilation.

Lung volumes are reduced after all types of abdominal surgeries. Functional residual capacity and vital capacity may fall to less than 50% of preoperative values on the first postoperative day but typically recover over the next week. Lack of sigh breaths (because of opioids, splinting, or both) and shallow tidal breathing prevents reactivation of surfactant, which, in turn, decreases functional residual capacity (FRC). Pain also compromises the patient's ability to cough and clear respiratory secretions. As a result, segmental, lobar, or even multilobar atelectasis can occur.

The incision used for the operation is an extremely important factor in postoperative care. *Thoracoabdominal* and *combined thoracic and midline incisions*, as encountered in some patients undergoing esophagectomy or reoperative surgery of the gastroesophageal junction or aorta, produce the greatest reductions in lung volumes (splinting) postoperatively. Upper midline incisions and subcostal or bilateral subcostal incisions are commonly used in the treatment of a variety of upper gastrointestinal and hepatobiliary procedures. Because *subcostal incisions* actually divide muscle in the upper abdomen, they are more likely to result in postoperative discomfort than are upper abdominal midline incisions.

Studies have not been able to show any difference between gastric and postpyloric feeding in the ICU with regard to complications such as pneumonia or outcomes such as length of stay and mortality. Although time to initiation of feeding may be quicker with gastric feeds, time to goal feeds (delivery of adequate nutrition) may be quicker via the post pyloric route.

The timing of nutritional support is somewhat controversial. In trauma patients, several studies have demonstrated that low-volume enteral feeds begun in the immediate postoperative period are both safe and efficacious. Experimental work suggests that intestinal anastomoses can heal well under these circumstances. However, many surgeons operating on an older, more chronically debilitated group of patients are less willing to feed patients until there is evidence of bowel function. Total parenteral nutrition can theoretically be started at any time following surgery, but in the immediate postoperative period (when patients are in the midst of an acute stress response) repletion of carbohydrate and protein stores by this mechanism is difficult. The value of early enteral feeding during the early postoperative time period is hypothesized to be due to its beneficial effects on the immune and "barrier" function of the gut.

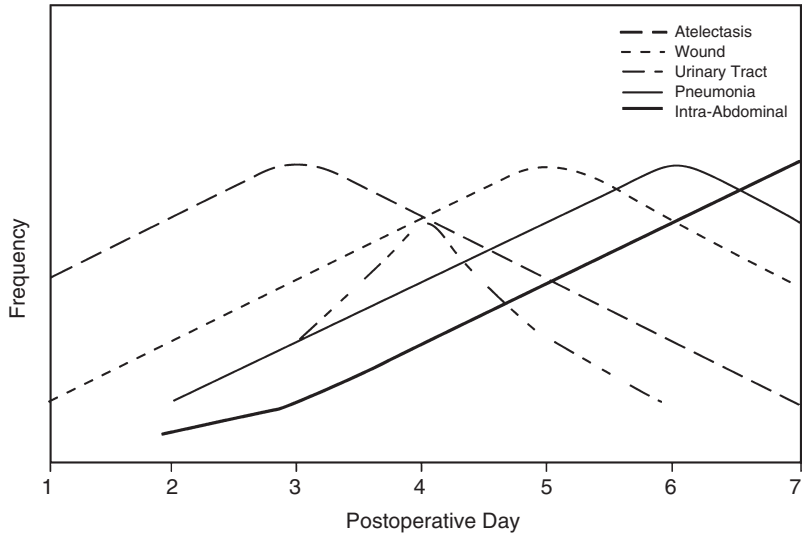


Figure 90.1 Schematic illustration of the time course and frequency of common causes of fever following major abdominal surgery.

Incisions centered around or below the umbilicus are typically used in elective lower GI and pelvic surgery. They have much less of an impact on postoperative pulmonary function than do subcostal or upper midline incisions. *Laparoscopic* procedures produce the least postoperative pain and may have a lower occurrence of pulmonary complications in the postoperative period. Unlike open abdominal procedures, however, laparoscopic surgery produces a marked decrease in FRC (which predisposes to basilar atelectasis) during the intraoperative period; particularly if high gas insufflation pressures are used.

FEVER

Fever is common in the postoperative period. It is stimulated by release of inflammatory cytokines (predominantly interleukin-1) from macrophages at sites of tissue injury and infection (Chapter 87). Figure 90.1 lists common sources of postoperative fever and their temporal relationship to surgery. The mnemonic "wind, water, wound, walking" applies to this set of relationships where *wind* refers to atelectasis, *water* to a urinary tract infection, and *walking* to deep venous thrombosis of the lower extremities (encountered most commonly between days 5 and 7 postoperatively). For the intensivist managing postoperative patients, one fundamental problem is to know when to pursue an extensive workup of a postoperative fever. In general, blood cultures are of little value in the first 48 hours following surgery.

URINARY TRACT INFECTION

Urinary tract infection (UTI) is the most common postoperative nosocomial infection, with gram-negative bacteria being the predominant pathogens. Most UTIs occur in the setting of bladder catheterization. Ten to 25% of patients with long-term catheterization (> 3 days) become infected, and 1% to 5% of patients having short-term catheterization (immediate operative period) become infected. Urinary catheterization and urinary tract infection are the predisposing factors most often associated with gram-negative bacteremia, which is twice as likely to originate

Most of the data comparing open versus laparoscopic surgery focuses on cholecystectomy and colorectal cases, and pulmonary complications are not always reported in detail. The laparoscopic approach has been shown to be associated with decreased postoperative pain, decreased length of stay, and improved spirometric parameters, but whether or not this leads to significant reductions in clinically important pulmonary complications remains an area of controversy.

from the urinary tract as from any other site. The single best way to reduce UTIs associated with urinary catheters is to limit device days, but, as with other drains placed in the operating room, it is important that the surgical and ICU team discuss the management before removal.

PNEUMONIA

Pneumonia is the second most common nosocomial infection encountered in the postoperative period. Multiple associated risk factors have been identified, including age > 70 years, upper abdominal surgery, depressed level of consciousness, use of H_2 histamine receptor blockers and proton pump inhibitors, and exposure to improperly sterilized respiratory care devices. Occult aspiration of neutralized gastric contents and oral secretions plus colonization of the oropharynx by hospital-acquired bacteria likely account for the overwhelming proportion of gram-negative pneumonias encountered postoperatively. Definitive diagnosis requires the isolation of an organism from respiratory secretions. However, in the absence of this condition, the presence of fever, leukocytosis, and infiltrate on the chest radiograph should all raise suspicion for this diagnosis (Chapter 14).

WOUND INFECTIONS

The risk of wound infection is directly correlated with the classification of operation. Operations may be classified as clean, clean contaminated, contaminated, and dirty. Obesity, old age, history of diabetes, other sites of infection, and duration of surgery also correlate with increased rates of wound infection. Redness, pain, swelling, fever, and drainage from the wound site indicate the presence of an infection, usually between the third and seventh postoperative days. *Staphylococcus aureus* remains the most common isolate, although gram-negative and mixed flora infections can also be seen after abdominal surgery. Opening the wound to facilitate drainage is the mainstay of therapy. Antibiotics are indicated if significant cellulitis is observed, if there are systemic signs of infection, or if a major soft tissue infection is suspected.

Aggressive, necrotizing *abdominal wall soft tissue infections* caused by hemolytic streptococci and clostridial species may produce high fevers in the early postoperative period (see Figure 90.1). These may be devastating if not diagnosed promptly. For this reason, although fever is common in the immediate postoperative period, it is imperative to inspect the wound/incision if high fevers occur during the first 24 to 48 hours. These life-threatening infections may manifest with drainage of thin, tan fluid, bullae appearing in the surrounding skin, or the skin may become dusky and crepitant. Such infections are rare, but when present they require immediate institution of parenteral antibiotics and, more important, prompt surgical debridement (see Chapter 66).

ILEUS

An ileus is defined as a delay in the return of antegrade intestinal peristalsis. It is an operational definition because the time course to return of function varies after operation. The small bowel is usually first to recover motility after major abdominal surgery, followed by the stomach and finally the colon. Preoperative peritonitis, extensive retroperitoneal dissection, reoperative surgery, and pancreatitis are all associated with a delay in return of peristalsis. Opioids, phenothiazines, and anticholinergic medications are also associated with ileus (Chapter 40). Signs of ileus include a distended abdomen, usually with diminished to absent bowel sounds, but rarely with substantial pain. Plain radiographs or computed tomography (CT) scans of the abdomen will show global bowel distention without a definitive transition zone (the latter would be indicative of obstruction). Treatment is largely supportive with nasogastric tube decompression and IV fluid hydration while keeping the patient NPO. Prokinetic agents such as metoclopramide

and erythromycin may be helpful, but only after mechanical bowel obstruction has been ruled out radiographically. In addition, attention should be targeted at cessation of agents that may be contributing to ileus. Peripherally acting μ-opioid receptor antagonists (PAMOR) are a class of drugs designed to reverse opioid-induced side effects on the gastrointestinal system without compromising pain relief.

THROMBOEMBOLIC DISORDERS

Deep vein thrombosis may complicate abdominal surgery in as many as 30% of patients. All patients undergoing abdominal surgery should receive appropriate prophylaxis against deep vein thrombosis, ideally prior to induction of general anesthesia. The presence of malignancy, preoperative bed rest, significant trauma, pelvic surgery, and prior history of thromboembolic disease are all additional risk factors. Prophylaxis with subcutaneous heparin (fractionated or unfractionated) or use of a pneumatic compression device on the lower extremities is indicated. Prophylaxis should be continued until the patient is ambulating. In high-risk patients, routine surveillance in the postoperative period using duplex ultrasound may be warranted and, in very high-risk trauma patients, prophylactic vena cava interruption may be warranted, although this is controversial.

HEMORRHAGE AND HYPOTENSION

Bleeding following abdominal surgery is usually not subtle. It may manifest as a GI bleed (bloody NG drainage, hematemesis, or hematochezia). Passage of a small amount of blood from the intestinal suture line is not unusual and may be observed in the early postoperative period. This type of bleeding usually stops spontaneously, but if it persists it may necessitate an angioembolization of the feeding artery. Gastrointestinal bleeding not thought to be related to a new anastomosis is managed in the same fashion as that for nonoperated patients. Intra-abdominal bleeding is harder to diagnose but should be considered in any postoperative patient with hypotension. Intra-abdominal hemorrhage is in some cases self-limited but often may necessitate a return to the operating room if hemodynamic instability persists despite resuscitation or if hemoglobin levels continue to fall. Often the diagnosis of intra-abdominal bleeding can be aided by examination of the effluent from any abdominal drains that were placed. A change in the quality of effluent from clear to bloody and an increase in volume may be noted, although the absence of these findings does not rule out bleeding as drains may be clogged or bleeding may occur at a location distant from the drain. When postoperative bleeding occurs, attention must be directed to correction of coagulopathy because even minor hemorrhage may not abate in the presence of a coagulopathy. Pharmacologic anticoagulation (including deep venous thrombosis [DVT] prophylaxis) should be held in the presence of postoperative hemorrhage until control is obtained. A systemic approach to postoperative hypotension is recommended (see Figure 90.1).

Intra-abdominal Sepsis

Patients undergoing major abdominal surgery occasionally experience postoperative *intra-abdominal sepsis*. Those at greatest risk are the immunosuppressed, malnourished, and elderly. Clinical manifestations of intra-abdominal sepsis include fevers beyond 5 days postoperatively, persistent leukocytosis, a failure to mobilize third space fluid or new fluid requirement, persistent ileus, unexplained mental status changes, and "remote" organ system dysfunction, such as acute kidney injury or the acute respiratory distress syndrome. Some patients may develop a new abdominal complaint that may facilitate the choice of further diagnostic studies.

Diagnostic studies directed by clinical findings or laboratory abnormalities yield a higher success rate than those performed in response to nonspecific elevations of fever, white blood cell

count, and organ system failure. The presence of two gram-negative enteric organisms in blood cultures should be considered, until proven otherwise, a result of an intra-abdominal pathology.

If acalculous cholecystitis is suspected, a portable right upper quadrant ultrasonography is the diagnostic test of choice. Management of acalculous cholecystitis includes percutaneous drainage of biliary contents or surgical removal of the gallbladder. In critically ill patients, ultrasound-guided percutaneous drainage is considered by some to be the procedure of choice.

Unless there is strong suspicion for specific pathology, computed tomographic scans performed within the first 5 days after abdominal surgery are unlikely to provide useful information. Laparotomy may be indicated as both "diagnostic and therapeutic." However, in the absence of strong evidence from an imaging study or a focal finding on physical examination, the yield of nondirected surgical explorations is low.

As with all cases of sepsis, the keys to a successful outcome are adequate and timely antibiotic coverage and source control. When imaging studies reveal a focus of intra-abdominal sepsis, broad-spectrum antibiotics should be initiated and efforts should be directed toward eliminating the source of infection. For patients with intra-abdominal fluid collections suggestive of infection, percutaneous drainage and culture of the fluid should be attempted when possible. For patients with uncontrolled sources of sepsis such as a leaking enteral anastomosis or an abscess that is not amenable to percutaneous drainage, surgical reexploration may be the only option.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 91

Major Tissue Flaps

Stephen J. Kovach ■ David W. Low

Patients undergoing a wide variety of major flap reconstructions warrant postoperative monitoring in an intensive care unit (ICU) setting to monitor flap viability, provide adequate hemodynamic support, and rapidly recognize compromised perfusion. Because early recognition of malperfusion can result in the salvage of autografts in most patients, the ICU clinician must be familiar with the early signs and symptoms of impending ischemia.

Flap Types

A flap refers to a surgically created peninsula or island of tissue that is at least partially detached from its original site and transposed to an adjacent or distant site. It is a commonly used technique to repair defects in plastic surgery. Tissue types for flaps include skin and subcutaneous tissue, fascia, muscle, bowel, omentum, or bone, or combinations of several tissues, such as a myocutaneous flap. The anatomic vascular supply to these flaps influences the method of flap transfer and dictates which parameters are necessary to monitor postoperatively to ensure flap viability.

Skin (and its subcutaneous tissue) that is transposed to an adjacent area without being detached is a *skin flap*. Generally, the length of a skin flap should equal its width to provide adequate perfusion. If there is no known vessel running within the flap, it is a *random flap.* If there is a vascular pedicle running through the flap, either in the subcutaneous layer or just above the fascial plane, it is an *axial pattern flap*, and its length can be significantly longer than its width. If the skin receives its blood supply from the underlying muscle via perforating vessels, it is a *myocutaneous flap*, and the skin can survive as an island.

Muscle or myocutaneous flaps, when mobilized with preservation of the vascular supply and transposed to the desired site without disrupting their vessels, are *pedicled flaps*. They remain attached to the patient and are limited by the available regional tissues that can be transferred to the site to be reconstructed. Their ability to reach the defect are limited by the pedicle length. Alternatively, when the muscle or myocutaneous flaps are moved to distant sites and their vessels are divided and reanastomosed to recipient vessels, they are referred to as *microvascular free flaps.*

Complications of Flap Surgery

Both the recipient and the donor sites of flaps are subject to the problems of any operative wound, such as bleeding, hematoma, suture line dehiscence, infection, and localized edema (Table 91.1). Because many patients receive perioperative anticoagulation, *hematoma formation* is a distinct risk because flap "harvests" result in large raw surfaces at the donor site.

Postoperative edema can severely compromise flap perfusion and stress suture lines. The operated site should be elevated above the level of the heart, if possible. The use of corticosteroids during flap harvest and early postoperatively to decrease flap edema remains controversial.

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Microvascular dissection of an island of skin and fascia based on a deep vessel that spares the underlying muscle has been termed a *perforator flap. Skin grafts* are not considered to be flaps because they survive initially by diffusion rather than by direct perfusion.

Other tissues can also be transferred as pedicled flaps or as free flaps, including omentum, fasciocutaneous flaps (radial forearm, anterolateral thigh, and transverse scapular flaps), bone (fibula, scapula), and bowel (jejunum). The success of the operation depends on establishing a reliable arterial inflow and venous outflow.

Replantation usually involves the reattachment of a finger or thumb: scalp, ears, lips, hands, feet, penises, and rare facial avulsions have also been salvaged. If the amputation is incomplete, but the vessels are transected, the repair is a *revascularization.* As with a microvascular free flap, success depends on the restoration of adequate arterial and venous flow.

In the ICU, drains should be "stripped" hourly—that is, the drain is compressed manually along its length in a proximal-to-distal direction to remove clots and enhance drainage. The aim of "stripping" is to decrease the risk of hematoma and seroma formation and to promote obliteration of the donor site dead space. An unexplained drop in hemoglobin may be secondary to unrecognized donor site bleeding. Hematoma formation at the recipient site can occlude venous outflow, leading to venous congestion and flap loss.

TABLE 91.1 ■ **Risk Factors for Flap Ischemia in the Immediate Postoperative Period**

Hematoma, Bleeding	***Malpositioning of Patient***
Donor site or sites	Increased tension on vascular pedicle
Recipient site	Compression of vascular pedicle
Anticoagulation-related	Increased dependent edema
Ischemia Caused by Arterial Obstruction	Potential pressure necrosis
Vasoconstriction, vasospasm	***Other Generic Factors***
Twisted or kinked pedicle	Anemia
Excessive traction	Edema
Thrombosed anastomosis	Infection
Ischemia Caused by Venous Obstruction	Hypothermia
Twisted or kinked pedicle	Hypovolemia with hypotension
Excessive traction	
Compression by hematoma or flap edema	
Thrombosed anastomosis	

Flap ischemia is the most devastating complication after flap surgery and can be due to arterial or venous obstruction, or both. In the case of pedicled flaps, ischemia may result from torsion of the vascular pedicle, increased tension on the pedicle as the tissues swell, or improper postoperative positioning that stretches or occludes the pedicle. The surgeon should clearly specify any restrictions in activity or positioning in the ICU postoperative orders. With microvascular free flaps and replantations, flap ischemia in the first 48 hours may be due to a technical problem that is correctable, and a prompt return to the operating room for reexploration should be considered.

Flap Monitoring: Subjective Methods

Color

A skin flap or a skin island of a myocutaneous flap (Figure 91.1) should be the same color (or slightly more pink) as the adjacent skin from which it was harvested. If it is hyperemic and purple, however, the venous outflow may be occluded. If it is mottled or extremely pale, the arterial inflow may be compromised. Of note, skin color changes in darkly pigmented patients may be difficult to discern.

A monitoring flap is a small externally visible portion of a buried flap that serves as an indicator of the vascular status of the deeper flap. It is usually a small skin island but may also be a segment of externalized jejunum. The external component should be at least 1 × 2 cm in size to permit accurate color assessment.

In contrast to skin flaps, color is not a reliable indicator for skin-grafted muscle flaps, because the skin graft has no initial perfusion.

Capillary Refill

It should normally take about 1 to 2 seconds for the color to return after manual blanching of the skin. Flaps with venous congestion show immediate refill, whereas flaps that are slow to fill may have compromised arterial inflow. Capillary refill may be difficult to assess in patients with darkly pigmented skin. Importantly, a skin graft normally has no capillary refill in the first 4 to 5 days after implantation as it takes this amount of time for vessels to grow and reperfuse the graft.

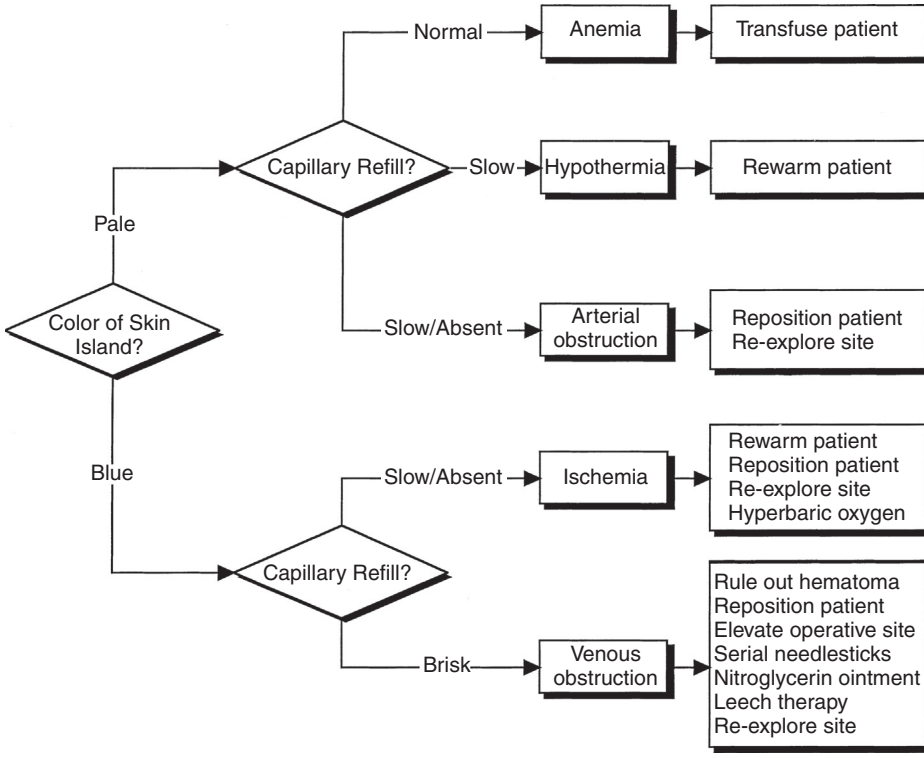


Figure 91.1 Schematic flow diagram for the evaluation and management of a threatened flap with a skin island visible.

Temperature

Flaps are often cooler than the surrounding native skin, making absolute temperature an unreliable indicator. A change in temperature, however, may indicate vascular compromise, and a temperature probe is more reliable than palpation alone.

Tissue Turgor and Flap Contour

Most flaps become edematous in the immediate postoperative period with edema reaching a maximum at 24 to 48 hours. Flaps that appear extremely tense and protruding may have venous congestion or an underlying expanding hematoma that requires evacuation. Venous occlusion in the face of persistent arterial inflow can result in sudden bleeding and swelling from the underside or edges of a flap as the vascular congestion decompresses through previously cauterized or clotted peripheral veins. Large flaps with a venous occlusion or thrombosis may accommodate significant amounts of blood within the parenchyma of the flap, and the diagnosis of venous thrombosis of the flap is sometimes difficult to discern from a hematoma. Both may result in a swollen flap with external signs of vascular compromise. Previously swollen flaps that appear soft or desiccated may have an arterial occlusion.

Pulse

A palpable pulse is not usually present in most flap reconstructions because the vessels are usually too deep or too small to be detected. Occasionally, when a large-diameter vein graft such as the

saphenous vein is used to connect a flap with a distant blood supply, the vein graft may have a palpable pulse that can be monitored.

Needle Stick

Bright red blood oozing from a punctured skin island or muscle flap suggests continued normal perfusion. Cyanotic blood that then becomes redder suggests venous hypertension that is temporarily relieved by the egress of blood from the engorged flap. Absence of pinprick bleeding and a persistent hole after withdrawal of the hypodermic needle signals a lack of arterial flow and reduced tissue turgor.

FLAP MONITORING: OBJECTIVE METHODS

Flow Monitoring

Intermittent or continuous ultrasonic Doppler flow monitoring (Figure 91.2) is a frequently used method for assessing arterial patency in flap surgery. Doppler probes are widely available in the ICU for monitoring patients undergoing peripheral vascular surgery, and the same instruments can be used to assess the integrity of flaps, particularly in those patients undergoing microvascular free flap reconstruction. The surgeon should identify and mark a site so that ICU personnel can easily assess the pulse, at least hourly, for the first 48 hours postoperatively. A loss of Doppler signal mandates immediate notification of the surgical team. Use of the Doppler may be less reliable in areas such as the head and neck where other regional arteries can give a signal that may be mistaken for the flap pedicle. In some cases, a venous Doppler signal can also be monitored (venous "hum"), which varies with respiration and can be augmented by compressing the flap. Implantable

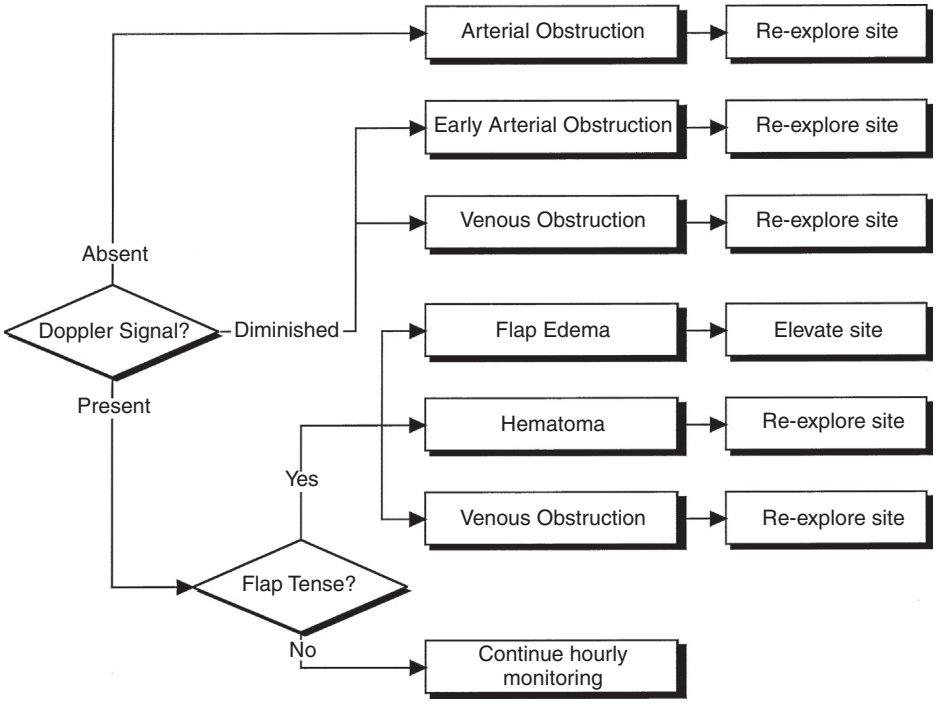


Figure 91.2 Schematic flow diagram for evaluation and management of a threatened microvascular free flap that is buried or skin grafted.

ultrasonic Doppler probes give a continuous waveform that can record both arterial and venous flow, but probe dislodgement or mechanical failure can give rise to false alarms.

Pulse Oximetry

Pulse rate and oxygen saturation can be continuously monitored in digital replants with a fingertip pulse oximeter. A loss of pulsations indicates arterial occlusion, and a drop in saturation (< 85%) suggests venous obstruction. Hemoglobin oxygen saturation has been monitored in intraoral free flaps using micro-lightguide spectrophotometry.

Surface Temperature Probe

Temperature-sensing electrodes, or even adhesive temperature strips, can be used to detect temperature changes. A fall of 1.0° to 2.0° C is consistent with vascular compromise. Surface temperature monitoring is more accurate with replanted digits when compared with flaps, which can be warmed by heat transfer from the underlying bed. Accuracy is also improved if the adjacent skin is monitored for temperature changes as well, because environmental factors and local hemodynamic changes can greatly affect cutaneous temperature reading at both sites. Thermocouple probes can also be implanted adjacent to vascular pedicles to monitor buried flaps. In most centers, however, temperature monitoring has been abandoned in favor of alternative monitoring devices.

Generic Postoperative Management

FLUID MANAGEMENT AND BLOOD TRANSFUSIONS

Patients must remain well hydrated to maintain adequate perfusion pressure and fluid volume in the microvasculature of the flap. They must also be kept warm to decrease peripheral vascular resistance and vasoconstriction. The use of vasopressors to maintain blood pressure is deleterious to flaps because they cause peripheral vasoconstriction and can compromise the vascular beds of the flap.

With microvascular surgery, a certain degree of hemodilution is desirable to decrease blood viscosity. Isovolemic hemodilution is the goal. In general, hemoglobin levels as low as 7 or 8 g/dL is safe as long as patients remain asymptomatic.

ANTICOAGULATION AND THROMBOLYSIS

Anticoagulation is not routinely used for pedicled flaps aside from routine prophylaxis against deep venous thrombosis. Most microsurgeons do not routinely use systemic full anticoagulation for free flap surgery unless there is a concern for vascular compromise intraoperatively, the patient is at high risk (traumatized or irradiated tissues), or the patient requires reexploration for vascular occlusion. In general, the risk of bleeding complications with anticoagulation must always be considered and weighed against the risk of vascular thrombosis.

Heparin

When indicated, patients are usually administered a bolus of intravenous heparin intraoperatively at the time of vascular anastomosis and a continuous infusion is given postoperatively at therapeutic or subtherapeutic doses. The partial thromboplastin time should be followed if heparin is given in therapeutic doses (Chapter 77).

Aspirin

Aspirin inhibits the release of cyclooxygenase from platelets, blocking the subsequent formation of thromboxane A_2. As an antiplatelet agent, low-dose aspirin (3 to 5 mg/kg/day) may be given

Some institutions have laser Doppler instruments, which use light instead of sound waves to detect red blood cell motion. They are placed on the skin surface overlying or next to the vascular pedicles to provide continuous monitoring. However, their sensitive fibers may give false alarms if they become encrusted with blood and secretions or if the patient moves. Implantable Doppler probes may have their greatest utility for monitoring buried flaps because such flaps cannot be reliably followed with surface probes.

Monitoring Partial Pressure of Oxygen

Transcutaneous pO_2 monitoring with a surface electrode is available in some institutions (e.g., for neonatal monitoring) and has applicability in monitoring skin flaps or myocutaneous flaps. It is not useful for skin-graft muscle flaps or for buried flaps. Additionally, the electrode heats up the skin and must be moved periodically to prevent possible burn injuries.

A pO_2 catheter microprobe has also been used to successfully monitor flaps with no false positives or negatives. A rapid fall indicates arterial compromise, whereas a slower fall is more consistent with venous congestion.

Fluorescein

Intravenous administration of fluorescein (10 to 20 mg/kg) and use of a Wood lamp to assess fluorescence may have utility in intraoperative flap assessment, particularly in determining peripheral flap viability. Routine ICU use for flap monitoring (1.5 mg/kg intravenously, assessed every 2 hours with a dermal fluorometer), however, is unusual and can only be performed with skin flaps or myocutaneous flaps. Side effects of fluorescein include nausea, vomiting, hypotension, and, rarely, anaphylaxis.

Color-Duplex Ultrasound

High-resolution color-duplex ultrasound has been reported as a useful non-invasive means of monitoring buried free flaps, particularly in the setting of head and neck reconstruction with significant postoperative edema, where surface Doppler probes may be unreliable. This is a static rather than a continuous study and requires the services of a licensed vascular technician, but it may resolve the clinical dilemma of whether or not to reexplore a flap reconstruction if pedicle patency can be demonstrated by color-duplex ultrasound. A potentially compromised flap is a surgical emergency, however, and exploration should not be delayed if duplex cannot be performed in a timely manner.

Experimental Monitoring Techniques

Green light photoplethysmography uses a diode to transmit green light into tissues. The reflected light from hemoglobin is analyzed and reportedly can detect venous or arterial compromise almost immediately. Microdialysis uses a catheter to sample glucose, glycerol, and lactate from the reconstructed flap. A decrease in glucose, with an increase in lactate and glycerol, is consistent with flap ischemia.

for up to a month beginning on the day of surgery. The desirable effect of aspirin is offset by its inhibition of prostacyclin generation by endothelial cells at higher doses.

Low-Molecular-Weight Dextran (10% Dextran 40)

As a polysaccharide available with a mean molecular weight of 40,000 d, low-molecular-weight dextran was initially used as a colloid for intravascular volume expansion. In addition to decreasing blood viscosity, it has an antiplatelet effect and also depresses factor VIII activity. It often is started intraoperatively with a loading dose of 40 mL then given as a continuous drip at 20 to 30 mL/h. Duration and tapering schedule vary according to surgeon.

Pentoxifylline

Pentoxifylline is a vasoactive drug derived from xanthine. It increases red blood cell deformity, may cause smooth muscle relaxation, and also has an antiplatelet effect. It is usually started several weeks preoperatively (orally) to achieve its effects on red blood cells and continued postoperatively until the operative site is healed.

Urokinase

Urokinase is a thrombolytic agent produced by human kidney cells that converts plasminogen to plasmin, a fibrinolytic enzyme. It is usually reserved for localized infusion during intraoperative free flap reexploration. Although it is commonly used as a continuous drip in the ICU for patients with occluded peripheral vascular grafts, it is rarely, if ever, administered in this manner for flaps. After successful thrombolysis with urokinase, heparin is usually given as a continuous systemic infusion.

Managing the Compromised Flap

POSITIONING

Pedicled flaps are rarely subject to arterial occlusion, but they may suffer arterial vasospasm, venous congestion, or distal ischemia. Malpositioning of the flap can cause unnecessary tension and result in tissue malperfusion. If the flap remains purple or blue but with brisk capillary refill, elevation of the flap may improve venous return and decrease flap edema.

VASODILATORS

Persistent vascular congestion may respond to nitroglycerin, a vascular smooth muscle relaxant with a greater effect on the venous than the arterial vasculature. Topical application, rather than intravenous infusion, is the usual mode of delivery.

OTHER INTERVENTIONS

Distal ischemia is usually allowed to demarcate, requiring subsequent flap debridement. Other maneuvers to maximize flap viability include the use of hyperbaric oxygen, if available, and the application of small felt pads soaked in heparin to promote continued venous oozing between needle pricks and the application of *medicinal leeches*. Leeches (*Hirudo medicinalis*) are usually available through the hospital pharmacy. They avidly attach to the site of a needlestick and begin to suck. After the leech detaches, the site bleeds because of a natural anticoagulant in the leech saliva (hirudin) that inactivates thrombin. New leeches are applied when the oozing subsides or if the flap remains engorged. Hemoglobin should be monitored during the course of leech therapy (which may last more than 5 days as new venous collaterals are formed), as blood loss

can be significant. Patients receiving leech therapy require antibiotic coverage against *Aeromonas hydrophila,* a symbiotic bacterium in the leech gut.

SURGICAL MANEUVERS

Venous occlusion in the patient with a microvascular free flap usually requires intraoperative reexploration and revision of the anastomosis sometimes with vein grafts. While waiting for the operating room to receive the patient, however, the surgeon may elect to remove sutures in an effort to decompress a possible hematoma that may be occluding the vessels. This maneuver alone may restore flow if the vessels are not thrombosed.

If there is an obvious clot in the vein, transecting the vein and administering a bolus (5000 units) of intravenous heparin may flush out the clot and restore normal circulation. The venous anastomosis can then be revised in the operating room. If no suitable vein repair can be performed, as may be the case with digital replants, leech therapy is usually instituted.

If the arterial Doppler signal becomes fainter but is still present, adequate systemic pressure and fluid status should be confirmed, and the flap should be kept warm to diminish vasospasm and constriction of the peripheral vasculature. If capillary refill is sluggish or absent and the pulse does not improve, patients should be readied for immediate reexploration. If there is suspicion of an expanding hematoma compressing the vascular pedicle, however, removal of a few key sutures at the bedside by the surgeon may restore the pulse. A decision should then be made as to whether or not a return to the operating room is necessary to reexplore the operative site.

Successful monitoring of the flap patient requires careful attention to detail. While no one method of postoperative flap monitoring is foolproof, vigilance and early recognition of vascular compromise are keys to success and the potential salvage of a compromised flap.

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CHAPTER 92

Major Vascular Procedures

Melissa L. Kirkwood ■ Edward Y. Woo

The care of patients with vascular disease in the intensive care unit (ICU) is challenging and requires an in-depth understanding of cardiovascular physiology and critical care. This chapter focuses on the perioperative care of the vascular surgery patient in general, as well as on particular aspects for some specific vascular procedures. Pertinent intraoperative factors will be highlighted when the condition or therapy has implications for the postoperative management.

General Approach to the Vascular Patient

Atherosclerosis is a systemic disease; therefore the majority of patients who suffer with peripheral vascular disease (PVD) also have coexisting coronary artery disease (CAD). Furthermore, patients with vascular disease frequently have a history of tobacco abuse, which often results in significant underlying respiratory disease. Hypertension, diabetes mellitus, and some degree of renal insufficiency are additional conditions commonly associated with PVD. Because these conditions are associated with morbidity and mortality after major vascular reconstruction, the preoperative evaluation and preparation of the vascular surgery patient should address both the underlying vascular disease and these associated conditions.

CORONARY ARTERY DISEASE

Cardiac events represent the most common cause of significant morbidity and mortality following major vascular surgery. In a large prospective cohort study involving more than 1400 patients undergoing major, nonemergent, noncardiac surgery, factors that were independently associated with myocardial infarction included preexisting CAD, age greater than 75 years, and a planned vascular surgery operation. The prevalence of CAD among vascular patients approaches 50%, and the frequency of triple-vessel CAD in these patients ranges from 15% in asymptomatic patients to 44% in those with symptoms.

Despite the high incidence of coronary artery disease, the benefits of routine preoperative non-invasive cardiac testing as well as pre-emptive coronary revascularization remain unclear. The positive predictive value of non-invasive imaging has uniformly been shown to be low and the test often does not provide information beyond that which can be obtained by assessing simple clinical risk factors.

RESPIRATORY DYSFUNCTION

Because vascular reconstructive procedures are frequently long, require a general anesthetic, and use abdominal or thoracic incisions, postoperative respiratory complications are common. Patients with vascular disease often have preexisting chronic obstructive pulmonary disease (COPD) from tobacco abuse, which increases the risk for postoperative complications as well.

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As part of the preoperative evaluation, all patients require an imaging study to assess the extent of their vascular disease. Duplex ultrasound scans offer a non-invasive alternative; however, more extensive evaluation with computed tomography angiography (CTA) scans, magnetic resonance angiography (MRA), or contrast arteriography is often necessary. Whereas MRA was initially thought to avoid the risk of nephrotoxicity that accompanies iodinated contrast agents, an accumulating number of reports have documented the development of nephrogenic systemic fibrosis following the use of standard and high-dose gadolinium-containing contrast agents in patients with decreased renal function. Therefore, in addition to determining the patient's baseline renal function, a risk benefit analysis weighing the increased diagnostic accuracy of these tests with the possibility of further renal deterioration should be performed in all patients with diminished renal function prior to the administration of intravenous contrast media.

This high rate of disease leads to a perioperative myocardial infarction rate ranging from 3% to 17%. As a result, coexistent coronary disease and perioperative cardiac events account for 25% to 70% of the early and late morbidity and mortality that accompany vascular reconstructive surgery. In addition to a comprehensive history and physical exam, it is also important in the preoperative evaluation to assess the patient's functional capacity. The inability of patients to perform their activities of daily living put them at increased risk for a perioperative cardiac event. Thus, a routine electrocardiogram should be obtained on all patients with vascular disease as part of the preoperative evaluation.

Because of the high prevalence of asymptomatic CAD, historically, most vascular surgeons prefer their patients undergo formal evaluation of cardiac function before proceeding with elective major vascular reconstruction. The most commonly used non-invasive tests to evaluate cardiac function include exercise testing, radionuclide ventriculography, echocardiography, dobutamine stress echocardiography, and dipyridamole thallium scintigraphy. Coronary angiography is performed if non-invasive testing shows evidence of myocardial dysfunction or ischemia. If angiography demonstrates significant CAD, coronary angioplasty or bypass grafting may be required before proceeding with elective vascular reconstruction. However, the relative urgency of the indicated vascular surgery must be considered because preoperative coronary revascularization has been shown to significantly postpone the intended vascular procedure.

They do, however, significantly increase preoperative cost. In a large randomized trial evaluating coronary artery revascularization before elective major vascular surgery, no significant difference was noted in perioperative myocardial infarction or mortality between the groups who were randomized to either coronary revascularization or no revascularization prior to the vascular procedure. This suggests that the routine strategy of coronary artery revascularization before elective vascular surgery among patients with stable cardiac symptoms should not be universally recommended. The American College of Cardiology in collaboration with the American Heart Association published guidelines in 2007 that include a stepwise algorithm for determining preoperative cardiac risk based on patient and surgery risk factors undergoing noncardiac surgery (see http://circ.ahajournals.org/content/116/17/e418.full; accessed July 23, 2012).

A careful preoperative history and physical examination must be performed in all patients to screen for COPD and other pulmonary diseases. All patients undergoing major vascular reconstruction should undergo chest radiography. If there is clinical or radiographic evidence of underlying pulmonary disease, arterial blood gas determinations and bedside spirometry or formal pulmonary function testing should be performed. Preoperative treatment with bronchodilators or inhaled or systemic corticosteroids is commonly used to optimize the functional status of patients with COPD before elective surgery. Finally, smokers should be strongly encouraged to abstain from tobacco use for at least 2 to 4 weeks (and preferably longer periods of time) before elective surgery. Observational studies have suggested that abstinence from smoking decreases the risk of perioperative pulmonary complications including respiratory failure, prolonged ICU admission, and pneumonia.

In patients with significant pulmonary dysfunction, it may be preferable to avoid general anesthesia, if possible. Spinal or epidural anesthesia is a frequently used alternative, particularly for lower extremity revascularization procedures. Additionally, a retroperitoneal approach can be used instead of the standard transabdominal approach for some aortic procedures. The retroperitoneal incision results in less postoperative pain and pulmonary dysfunction compared with an abdominal incision. Effective postoperative pain control is essential in order to prevent postoperative pulmonary complications. Pulmonary toilet, including coughing and incentive spirometry, is critical in the postoperative period and is made possible with effective relief of incisional pain. Epidural analgesia has become the method of choice for pain control postoperatively in patients undergoing thoracic or abdominal vascular procedures (Chapter 87).

RENAL INSUFFICIENCY

Renal insufficiency is frequently present in patients with PVD. This may be the result of atherosclerotic renal artery occlusive disease, diabetic nephropathy, or uncontrolled hypertension. Vascular surgical patients with preoperative kidney dysfunction are at increased risk for developing postoperative acute renal failure (ARF). The incidence of postoperative ARF ranges from 1.7% to 25% and, when present, is associated with an increased risk of perioperative infection and mortality.

MONITORING

Because of the potential for hemodynamic instability, patients undergoing aortic or carotid surgery should have continuous blood pressure monitoring with an indwelling arterial catheter. The decision to place a pulmonary artery catheter should take into account the baseline cardiac status of the patient, the magnitude of the operative procedure to be performed, and the anticipated hemodynamic disturbances during and after the operation.

Hemoglobin, hematocrit, platelet count, and coagulation studies must also be monitored closely during the postoperative period. Blood pressure must be closely followed and tightly controlled to avoid wide fluctuations in either direction. Hemodynamic instability should be immediately assessed, and management should proceed in a stepwise and thoughtful manner (Figure 92.E1).

Procedure-Specific Care: Abdominal Aortic Reconstruction

All patients require monitoring in the ICU after open aortic reconstruction, with many patients requiring mechanical ventilation overnight. Cardiac complications are a major cause of postoperative morbidity and mortality, as previously described (see Figure 92.1). Invasive hemodynamic monitoring with a pulmonary artery catheter should be considered to direct fluid resuscitation and optimize cardiac function (Chapters 7, 8, and 11). Significant intraoperative blood loss and fluid shifts can result in hypotension in the postoperative period. Postoperative fluid requirements after aortic reconstruction may be significant because of large fluid shifts. Once the patient's volume status has been optimized, cardiac function can be augmented with inotropic drugs if hypotension persists. Significant postoperative hypertension may result in suture line bleeding and increase myocardial oxygen consumption and therefore should also be avoided. Postoperative hypertension should be treated with short-acting vasodilators such as nitroglycerin or nicardipine for rapid titration. Occasionally, hypertension can result from postoperative pain, which, when present, should be treated accordingly (Chapter 87).

Postoperative hemorrhage is usually the result of either a technical problem or an acquired coagulopathy. Many factors contribute to postoperative coagulopathy after aortic surgery.

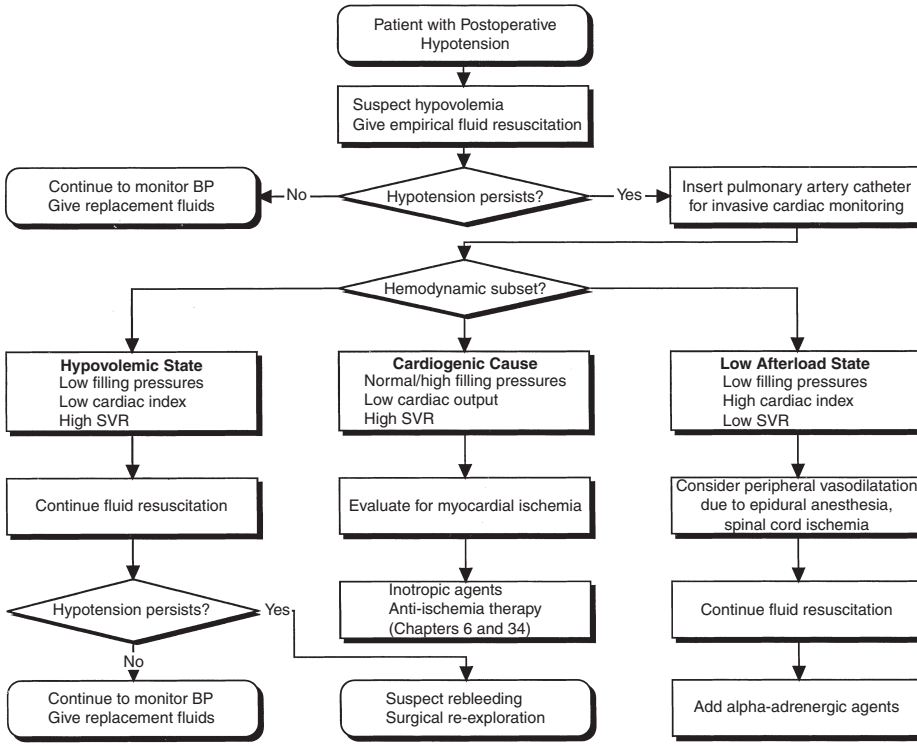


Figure 92.E1 Schematic flow diagram illustrating a general approach to the management of postoperative hypotension. BP, blood pressure; SVR, systemic vascular resistance.

Preventive strategies include identifying patients at risk, optimizing intravascular volume, and avoiding nephrotoxins. Common perioperative nephrotoxins include antibiotics that can be associated with acute interstitial nephritis often requiring dosage adjustments in patients with impaired creatinine clearance. Additionally, nonsteroidal anti-inflammatory drugs (NSAIDs) can cause ischemic acute tubular necrosis and acute interstitial nephritis by altering prostaglandin synthesis. Multiple studies and meta-analyses have attempted to determine if prophylactic strategies of intravenous hydration, *N*-acetylcysteine, or other agents reduce the incidence of contrast-induced nephropathy. Current evidence suggests that maintaining hydration with normal saline or sodium bicarbonate solutions, thereby ensuring adequate intravascular volume and sufficient renal perfusion, is the most beneficial strategy. If renal function deteriorates after a diagnostic procedure, elective surgery should be delayed to allow renal function to recover.

Two large randomized controlled trials, the Comparison of Endovascular Aneurysm Repair with Open Repair in Patients with Abdominal Aortic Aneurysm (EVAR-1) and the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial, both demonstrated endovascular aortic aneurysm repair to be a safe alternative to open repair with a clear short-term survival benefit. Although long-term results show that all-cause mortality is the same whether patients are treated with EVAR or open repair, the aneurysm-related mortality was lower in the EVAR group. However, the rate of reinterventions was significantly higher in the EVAR group. Overall, EVAR remains an attractive, less invasive option, given its shorter operative times and the avoidance of aortic cross clamping. Ongoing multicenter prospective randomized controlled trials are evaluating the role for EVAR versus open repair in healthy, asymptomatic patients.

Hypothermia, which can lead to the inactivation of clotting factors, is common with prolonged operative times and large fluid shifts. Other common causes of postoperative bleeding include decreased platelet function secondary to preoperative antiplatelet therapy, inadequate reversal of heparin with protamine sulfate, and development of a dilutional coagulopathy secondary to large intraoperative blood losses. In addition, in cases of prolonged supraceliac aortic cross clamp time, coagulation abnormalities can arise as a result of hepatic ischemia. Therefore, it is imperative to replace clotting factors and platelets as necessary and to normalize the body temperature as the first steps in the treatment of postoperative bleeding. If the patient has excessive blood loss or if the bleeding continues despite normal coagulation parameters, reoperation to look for technical causes of bleeding may be indicated.

Lower extremity ischemia after open aortic reconstruction is a well-recognized consequence of atheroemboli and occurs in 1% to 5% of patients. Limb ischemia following EVAR has also been reported to occur with a mean incidence of 5.1% and is most frequently the result of limb occlusion, although atheroembolization has also been reported. Complex aortoiliac anatomy—including tortuous, narrow, and calcified access vessels—has been proposed as a potential cause of limb occlusion following EVAR. The presence or absence of lower extremity pulses or arterial signals should be documented preoperatively and serve as a baseline to compare with in the postoperative period. The pulse exam should be reconfirmed prior to leaving the operating room and should be checked frequently in the postoperative period. The loss of peripheral pulses postoperatively demands urgent exploration and restoration of blood flow to the ischemic limb.

Clinically significant *intestinal ischemia,* most commonly affecting the rectosigmoid colon, occurs in 1% to 3% of patients after elective open aortic aneurysm repair. The diagnosis can be difficult because patients are often sedated and the incisional pain can mask the abdominal pain. The most common clinical signs of intestinal ischemia include bloody diarrhea, abdominal distention, peritonitis, metabolic acidosis, and hypotension. Because the sigmoid colon and rectum are almost always involved, the diagnosis can usually be made by sigmoidoscopy. A high index of suspicion is the key to early diagnosis. Cases of ischemia limited to the mucosa can be treated with supportive care, antibiotics, and close observation. Abdominal exploration, with resection of ischemic bowel and colostomy formation, is required for transmural ischemia. The overall mortality for aortic surgery complicated by clinically significant intestinal ischemia ranges from 37% to 60%. Cases of transmural ischemia and associated organ failure have been associated with even higher mortality rates.

Acute renal failure develops in 2% to 10% of patients after open abdominal aortic aneurysm (AAA) repair and is independently associated with mortality and prolonged length of hospital stay after major vascular surgery. Hypoperfusion and atheroembolization related to aortic cross clamping as well as perioperative hemorrhage increase the risk of acute renal failure. ARF requiring hemodialysis has been reported to occur in 0.5% to 2% of patients undergoing elective AAA repair, with an associated in-hospital mortality of 25% to 66%. Regardless of repair technique, maintaining renal blood flow by optimizing fluid status and cardiac output is the most effective way to both prevent and treat postoperative renal failure.

Spinal cord ischemia resulting in paraplegia is an uncommon but devastating complication after infrarenal aortic reconstruction. The fundamental cause of spinal cord ischemia is a loss of adequate blood supply to the distal spinal cord. It can result from prolonged aortic clamping, intraoperative hypotension, and atheromatous embolization. Interference with the pelvic circulation such as in oversewing or exclusion of lumbar and hypogastric arteries, either by open or endovascular techniques, has also been suggested to contribute to paraplegia.

If a patient develops paraplegia after aortic reconstruction, magnetic resonance imaging of the spinal cord should be performed immediately to rule out an epidural hematoma as a cause of the neurologic decline. If present, immediate neurosurgical consultation is required for decompressive laminectomy. If there is no epidural hematoma, efforts should be focused on therapies to

In emergent cases the incidence of intestinal ischemia increases to 10%. When routine postoperative colonoscopy is performed, the range of detected ischemic changes reaches 5% to 9% following elective surgery and 15% to 60% following rupture. Although EVAR has a lower rate of early postoperative mortality compared to open aortic repair, the incidence of clinically significant colonic ischemia is similar to conventional repair and ranges from 1.5% to 3%. Ischemia occurs most frequently in patients with occlusive disease of the mesenteric vessels, resulting from interruption of collateral blood flow to the intestine. The rectosigmoid colon is affected most commonly because of the frequency of disease in the inferior mesenteric and hypogastric arteries.

Endovascular aneurysm repair spares the ischemic insult to the kidneys that comes with aortic cross clamping and also is associated with less perioperative blood loss; however, nephrotoxicity can result from the intravenous contrast administered during the repair. Despite the necessary contrast load, EVAR has been associated with a 60% reduction in the risk of postprocedure ARF when compared to open aortic aneurysm repair.

The artery of Adamkiewicz is the major blood supply to the lower spinal cord and usually arises from a branch of the intercostal artery between T8 and Ll. Occasionally this artery may originate from the infrarenal aorta, accounting for the rare occurrence of spinal cord ischemia after infrarenal aortic reconstruction.

maximize blood flow to the spinal cord. Augmentation of blood pressure with vasoactive agents will increase the perfusion pressure to the spinal cord. If rapid improvement is not seen, consideration should be given to placement of a lumbar drain catheter to reduce the pressure surrounding the spinal cord.

Procedure-Specific Care: Carotid Artery Surgery

Surgery on the carotid artery is often complicated by significant hemodynamic instability. Manipulation of the baroreceptors in the carotid body can result in bradycardia with associated hypotension. In addition to surgical manipulation of the carotid baroreceptor, the surgical removal of the carotid plaque itself causes partial disruption of baroreceptor activity as the sensory nerve endings are stripped from the arterial lumen leading to hypertension and increased pressure instability. Technical factors, including cross clamping of the carotid artery, lead to a predictable pattern of reduced cerebral blood flow, which is accompanied by a compensatory increase in arterial pressure mediated by baroreceptor reflexes and an increase in sympathetic nervous system activity. This phenomenon is later reversed when the clamp is released and can result in profound hypotension in the immediate postoperative period. Patients undergoing carotid endarterectomy are at increased cardiovascular risk given their history of atherosclerosis and frequent fluctuations in blood pressure. These fluctuations are often poorly tolerated in this patient population and may contribute to myocardial or cerebral ischemia. Therefore, a careful neurologic examination should be performed after completion of the procedure before the patient leaves the operating room.

Blood pressure control is extremely important in the postoperative period after carotid endarterectomy. Hypertension (systolic blood pressure > 200 mm Hg or mean blood pressure > 35 mm Hg above baseline) has been noted in over 50% of patients. Such hemodynamic derangements may contribute to wound hematoma, hyperperfusion syndrome, intracerebral hemorrhage, and myocardial infarction. The pathophysiology of cerebral hyperperfusion syndrome is related to two interlinked mechanisms that both culminate in increased cerebral blood flow. Impaired cerebral autoregulation, coupled with postoperative elevated systemic blood pressure, create a hyperdynamic flow state that can have devastating consequences. Intensive hemodynamic monitoring and tight blood pressure control are essential to avoid this syndrome. Vasodilating agents such as nitroglycerine, nicardipine, and hydralazine may be deleterious in patients with increased cerebral blood flow and impaired autoregulation after CEA, as these agents tend to augment cerebral vasodilation. However, this theoretic disadvantage may be outweighed by the ability of these agents to efficiently control hypertension. Intravenous beta-blockers, such as labetalol, can be effective in controlling postoperative hypertension and should be titrated to effect. As soon as the patient is awake and neurologic function has been evaluated and found to be normal, patients who chronically take oral antihypertensives may resume their medications.

Hypotension also commonly occurs after carotid endarterectomy and has been documented in up to 50% of patients. When present, hypotension must be treated aggressively as reduced flow through the newly endarterectomized artery can contribute to a milieu supportive of thrombus formation and subsequent stroke. In addition, hypotension can reduce coronary perfusion leading to myocardial ischemia. Volume resuscitation should be the initial treatment. If hypotension is unresponsive to fluid replacement, cardiac function must be evaluated to rule out myocardial ischemia.

Postoperative stroke is perhaps the most devastating complication after carotid endarterectomy. Postoperative neurologic deficits can be the result of cerebral ischemia during carotid clamping, atheromatous or platelet emboli during the procedure, or thrombosis of the internal carotid artery. The patient should not leave the operating room until he or she has emerged from anesthesia and has moved all extremities. If the patient awakens with a neurologic deficit, the neck should be reexplored immediately to verify the patency of the internal carotid artery. Neurologic

The incidence of cerebral hyperperfusion syndrome following CEA is 1.9% and after CAS is 1.16%. This syndrome is characterized clinically with a deterioration of consciousness, confusion, and headache ipsilateral to the revascularized artery within a few days following carotid endarterectomy. A neurologic deficit may develop secondary to cerebral edema; however, it is usually transient. When present, symptoms can include hemiplegia, hemiparesis, aphasia, and obtundation. The most feared complication of hyperperfusion syndrome is intracerebral hemorrhage, which occurs in 0.37% of patients receiving a large series CEA and in 0.74% of patients receiving a CAS.

function must be monitored closely in the postoperative period. A patient who experiences a neurologic deficit in the early postoperative period that is appropriate to the operated side should have the patency of the internal carotid artery evaluated immediately. This can be carried out non-invasively by carotid duplex scanning or alternatively by arteriography. If such testing cannot be obtained quickly, a neck reexploration should be performed immediately. Rapid restoration of cerebral blood flow is the only way to reverse a neurologic deficit if the internal carotid artery is thrombosed. Neck exploration should not be delayed to obtain diagnostic testing.

Conclusion

The perioperative management of patients undergoing major vascular procedures can be challenging. It is essential to have a detailed understanding of the vascular anatomy, the procedure performed, and the complications particular to the operation. Anticipation and proactive measures taken to avoid wide swings in hemodynamic parameters are essential for an optimal outcome. Additionally, careful and frequent neurologic and vascular examinations should be undertaken in all such patients postoperatively. Any significant change in these parameters should prompt an immediate discussion with the vascular surgeon.

An annotated bibliography can be found at www.expertconsult.com.

Cranial nerve injury is another potential complication after carotid endarterectomy, and its reported incidence is highly variable. In the largest series of patients undergoing CEA in which neurologic assessment was performed both before and after surgery, the incidence of motor cranial nerve injury immediately postoperatively was 5.1%. The majority of the deficits resolved, with a residual nerve injury still present at 4-month follow-up in only 0.5% of patients. In this study the majority of motor deficits involved the hypoglossal, marginal mandibular branch of the facial and the recurrent laryngeal nerves. The hypoglossal nerve exits the skull through the hypoglossal canal coursing posterior to the carotid and internal jugular vein and subsequently passing medially across the internal and external carotid arteries where it can be injured. The hypoglossal nerve supplies motor innervation to the tongue and injury manifests as tongue deviation toward the injured side, inarticulate speech, and difficulty with mastication.

Injury to the marginal mandibular branch of the facial nerve typically leads to an ipsilateral lower lip droop and lip biting. This nerve emerges from the parotid gland and courses below the angle of the mandible toward the mouth, deep to the platysma muscle. Hyperextension of the neck and rotation to the opposite side cause this nerve to be more inferior and places it at increased risk for injury during superior extension of the incision and upward retraction. The vagus nerve exits the skull through the jugular foramen and descends into the carotid sheath posterolateral to the common carotid artery and internal jugular vein. Injury to the vagus nerve can occur during dissection, retraction, or carotid artery clamping. The recurrent laryngeal nerve can also be damaged by retraction as it lies within the tracheoesophageal groove. Clinical manifestations of recurrent laryngeal nerve injury range from mild symptoms of hoarseness and dysphagia to life-threatening airway obstruction resulting from bilateral recurrent laryngeal nerve injury.

The superior laryngeal nerve courses posterior to the carotid artery passing adjacent to the superior thyroid artery where it can be exposed to injury. Damage to the external branch of this nerve, which innervates the cricothyroid muscle, results in easy voice fatigue and an inability to create high-pitched sounds. It is essential to include a cranial nerve exam in the postoperative neurologic evaluation of the patient immediately following the procedure in the operating room.

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CHAPTER 93

Perioperative Care of the Morbidly Obese Patient

Nina M. Bowens ■ Noel N. Williams

Obesity has become a major health epidemic. Not only is it associated with significant comorbidities, but it also serves as an independent risk factor for early mortality. In a 2009-2010 survey, more than 50% of U.S. adults were overweight (body mass index [BMI] 25 to 29.9 kg/m^2), as many as one third were obese (BMI ≥ 30 kg/m^2), and up to 5% were morbidly (or severely) obese (BMI ≥ 40 kg/m^2).

As a result of the increasing prevalence of obesity in the United States, health care providers are caring for a greater number of morbidly obese patients undergoing both bariatric and non-bariatric surgical procedures. Optimal perioperative management requires the ability to accurately assess and treat multiple organ systems in order to reduce the likelihood of complications.

Physiology of Obesity

Adipose tissue releases numerous humoral mediators with broad spanning effects on metabolic, cardiopulmonary, and immune function. Morbid obesity itself has been compared to a state of critical illness with the associated chronic inflammation, hypercoagulability, and insulin resistance. Furthermore, the systemic alterations associated with obesity are significant and establish a paradoxical state of decreased reserve with increased physiologic demand.

Preoperative Evaluation

Morbidly obese patients are at increased risk for perioperative complications. Risk stratification remains difficult, however, as progressive organ dysfunction often goes undetected until the patient is faced with a surgical stress response. The Obesity Surgery Mortality Risk Score (OS-MRS) was developed as a tool to risk-stratify obese patients undergoing bariatric surgery. This system utilizes five patient characteristics that have been identified as independent risk factors for perioperative mortality, including (1) BMI ≥ 50 kg/m^2, (2) hypertension, (3) male gender, (4) significant risk factors for pulmonary embolism (such as pulmonary hypertension or previous venous thromboembolism), and (5) age ≥ 45. Predicted postoperative mortality risks are as follows: 0.2% to 0.3% for patients with zero or one risk factor, 1.1% to 1.3% for those with two or three risk factors, and 2.4% to 4.3% for those with four or five risk factors. Although this system was designed to risk-stratify patients specifically undergoing bariatric surgery, it is likely that similar attributes play a contributing role in many major abdominal procedures.

The American Heart Association (AHA) has developed specific guidelines for the preoperative cardiovascular evaluation of the morbidly obese patient for noncardiac surgery. In addition to a thorough history and physical examination, additional preoperative testing should be targeted according to symptoms and risk factors with the purpose of identifying undiagnosed comorbidities. Supplementary laboratory investigations should be tailored to the specific operation. General recommendations for preoperative screening include a complete blood cell count, comprehensive metabolic panel with liver function tests, coagulation panel, hemoglobin A1C, urinalysis, spirometry,

standard posterior-anterior (PA) and lateral chest radiograph (CXR), and an electrocardiograph (ECG). Given the magnitude of organ systems affected by obesity, each patient much be assessed on an individual basis with appropriate system-specific screening as indicated.

PULMONARY

Pulmonary dysfunction is highly prevalent among morbidly obese patients. Conditions such as obstructive sleep apnea, obesity hypoventilation syndrome, and pulmonary hypertension all result in severe alterations of respiratory physiology and significantly increase perioperative risk. Furthermore, morbidly obese patients are more likely to experience perioperative respiratory complications such as hypoxemia, pneumonia, and respiratory failure.

Obstructive Sleep Apnea (see Chapter 80)

Obstructive sleep apnea (OSA) is common among obese individuals and is a potentially fatal condition in the perioperative period if not identified and treated appropriately. The diagnosis should be suspected when patients (or their partners) report symptoms including snoring, frequent awakening from sleep with dyspnea, or daytime somnolence. Patients frequently experience apneic episodes resulting from upper airway obstruction secondary to excessive fat and redundant pharyngeal tissue. Large neck circumference is strongly predictive of clinically significant obstructive symptoms.

OSA significantly increases the risk for perioperative complications and postoperative respiratory failure. Apneic episodes are associated with an increased risk for aspiration, cardiac dysrhythmias, pulmonary hypertension, hypoxia, and hypercapnia. Several studies have suggested that OSA may be a positive predictor for an increased incidence of anastomotic leaks, prolonged hospitalization, and intensive care unit (ICU) admission.

Patients suspected of having OSA should undergo preoperative polysomnography testing. The degree and severity of OSA can be quantified during such testing by counting the number of times a patient develops apnea or hypopnea over a period of time—the so-called apnea-hypopnea index (AHI). By combining the AHI with more subtle sleep interruptions (respiratory event–related arousals [RERAs]), one can calculate the respiratory disturbance index (RDI). The RDI equals the number of RERAs, hypopneas, and apneas, all divided by the number of hours taken for the test. Continuous positive airway pressure (CPAP) or non-invasive assisted respiration (e.g., using bilevel positive airway pressure [BIPAP]) is recommended when patients demonstrate a significant respiratory disturbance index (RDI) > 25 (Chapter 3). Non-invasive ventilatory support is also indicated for patients who have apnea-induced comorbidities including pulmonary hypertension or cardiac dysrhythmias. Once the need for positive airway pressure support is established, it is recommended that patients have several weeks of use prior to their elective procedure. Patients with severe obstructive sleep apnea or an inability to tolerate CPAP/BIPAP may be considered for elective tracheostomy.

Obesity Hypoventilation Syndrome (see Chapter 80)

Obesity hypoventilation syndrome (OHS) is characterized by chronic hypoxemia and hypercapnia that worsens when asleep. The syndrome results from a restrictive lung pattern created by the excess weight of the chest wall with a predisposition to CO_2 retention. Obese patients demonstrate reduced spirometric measures including functional residual capacity and expiratory reserve volume as a result of poor chest compliance (Figure 29.1 in Chapter 29).

Chronic hypoxemia may eventually lead to compensatory polycythemia and increase the risk for venous stasis. Phlebotomy is recommended for patients with hemoglobin concentrations ≥ 16 g/dL. The state of chronic hypoxemia and secondary vasoconstriction often results in pulmonary hypertension. Patients with concomitant pulmonary hypertension and right-sided heart failure should be considered for prophylactic inferior vena cava (IVC) filter placement, as pulmonary embolism would be tolerated poorly.

Preoperative arterial blood gas evaluation is recommended for morbidly obese patients with a history of cardiopulmonary disease. Severe hypoxemia or hypercapnia may indicate a need for right heart catheterization. Preoperative medical optimization under the care of a cardiologist or pulmonologist is indicated in the setting of pulmonary hypertension with cor pulmonale.

CARDIAC

Obesity has been cited as an independent risk factor for cardiac disease. This is likely, at least in part, an epiphenomenon, as obese patients frequently suffer from other comorbidities including hypertension, hypercholesterolemia, diabetes, and altered respiratory physiology.

Assessment of cardiac risk in the morbidly obese patient should initially be based on history and physical examination. Historical information used to evaluate functional capacity and baseline cardiac function, however, may be difficult to interpret because of the deconditioning and respiratory problems that often accompany morbid obesity. The American College of Cardiology/American Heart Association has published guidelines that specify what further testing is warranted.

There is general consensus that morbidly obese patients should, at the very least, be screened with a preoperative ECG. Patients with more than one cardiac risk factor and decreased functional capacity may benefit from further non-invasive stress testing. Echocardiography or cardiac catheterization may be indicated in the obese patient with significant respiratory comorbidities or signs of heart failure. If abnormalities are identified, patients should undergo evaluation by a cardiologist with preoperative optimization as indicated.

ENDOCRINE

Diabetes is associated with increased perioperative morbidity and mortality. Morbidly obese patients often suffer from dysregulated glycemic control secondary to insulin resistance or frank diabetes mellitus. Furthermore, the stress response and elevated catecholamines induced by surgery typically exacerbate hyperglycemia.

Preoperative assessment should include a basic metabolic panel with blood glucose and hemoglobin A1C. Patients with diabetes should establish appropriate glycemic control with the assistance of their primary care physician or endocrinologist prior to operative intervention. Although there are no strict guidelines, blood glucose should generally be maintained between 80 and 150 mg/dL preoperatively and HbA1C < 7. The overnight fast or nil per os (NPO) status required prior to surgery mandates adjustment of hypoglycemic medications or insulin dosing to avoid perioperative hypoglycemia. Thiazolidinediones and insulin secretagogues should be held on the morning of surgery. Metformin has been associated with lactic acidosis and should be held 1 day prior to surgery. Long-acting oral hypoglycemics should be held 2 to 3 days prior to surgery. Patients who require insulin should continue their typical basal dosage to avoid ketoacidosis.

HYPERCOAGULABILITY

Obese patients are at high risk for venous thromboembolism (VTE). Not surprisingly, pulmonary embolism is the most common cause of early postoperative mortality following bariatric surgery. Many factors contribute to Virchow's triad of stasis, hypercoagulability, and endothelial injury.

Chronic hypoxemia with secondary polycythemia, limited activity, and poor venous return secondary to increased intra-abdominal pressure and IVC resistance contribute to and promote venous stasis. Inflammatory mediators released by adipocytes including fibrinogen and

plasminogen activator inhibitor along with decreased antithrombin III levels are partially responsible for the hypercoagulability seen in these patients. Nevertheless, in the absence of symptoms of deep venous thrombosis, routine preoperative screening with venous duplex ultrasonography is not indicated.

There is no specific protocol for preoperative VTE prophylaxis. General recommendations for bariatric procedures include unfractionated or low molecular weight heparin given 30 minutes to 1 hour preoperatively. The proper dosing regimen for heparin remains controversial; however, it is common practice to administer a preoperative dose of 5000 U of unfractionated heparin for patients with a BMI < 50 kg/m^2 and 7500 U for patients with a BMI ≥ 50 kg/m^2.

Prophylactic IVC filter placement should be considered in patients who are high risk for VTE or who have comorbidities that would make pulmonary embolism likely to be life threatening. Patients considered for preoperative filter placement include individuals with a history of thromboembolism, venous stasis, pulmonary hypertension, truncal obesity, BMI ≥ 60 kg/m^2, or a known hypercoagulable state.

Intraoperative Management

The morbidly obese patient may present considerable challenges to the anesthesiologist. Intraoperative management requires an in-depth understanding of the altered mechanics and physiology of the morbidly obese patient.

POSITIONING/PREOPERATIVE PREPARATION

Positioning the morbidly obese patient can be challenging. The excess weight of extremities and the often inadequate supportive equipment place the obese patient at high risk for peripheral nerve injury and pressure-induced soft tissue injury. Care should be taken to ensure that the patient is positioned and secured in the anatomically appropriate position with adequate padding at all pressure points. Extra-large operative beds may be required.

Pharmacologic thromboembolic prophylaxis should be continued intraoperatively along with intermittent pneumatic compression stockings, which should be in place and active prior to induction of anesthesia. The choice of preoperative antibiotic prophylaxis should be based on the nature of the surgical procedure and administered at least 30 minutes prior to incision. Given the propensity for large fluid shifts, the appropriate assessment of intravascular volume status necessitates Foley catheter placement.

AIRWAY AND VENTILATION

Prior to induction of anesthesia, patients should be preoxygenated with 100% oxygen. Positive end expiratory pressure (PEEP) of up to 10 cm H_2O may be applied via the mask in order to minimize dependent atelectasis. It is important to understand, however, that despite adequate preoxygenation the oxygen saturation will decrease rapidly because of the reduced functional residual volume within their lungs. As a result, if a difficult airway is anticipated, many anesthesiologists will not even attempt direct laryngoscopy and, instead, proceed initially with an awake fiberoptic intubation. That being said, contrary to popular belief, most morbidly obese patients have a very straightforward intubation if positioned properly. Although the classic "sniffing" position allows the optimal view for intubation in most patients, for those with morbid obesity this is often difficult because of the enormous amount of redundant soft tissue around the neck and chest. Placing a "ramp" (or "shoulder roll") beneath these patients (easily made with blankets) causes the oral, pharyngeal, and laryngeal axes to become appropriately aligned, usually allowing a good view of the vocal cords.

HEMODYNAMIC MONITORING

General anesthesia may result in significant hemodynamic changes in any patient, but these effects are often exaggerated in those with morbidly obesity. Morbidly obese patients often manifest varying degrees of diastolic dysfunction and may be very sensitive to changes in volume status. Consideration should be given for additional intravascular access and monitoring such as an arterial or pulmonary arterial catheter. Although the majority of patients may be adequately monitored with a large non-invasive blood pressure cuff, the anesthesiologists should evaluate appropriate venous and arterial access sites preoperatively.

The anesthesiologist must also be aware of hemodynamic alterations specific to the surgical procedure. Several factors may contribute to decreased cardiac function in the intraoperative setting including anesthetic effects, blood loss, and fluid shifts. Although the physiologic alterations associated with major open abdominal surgeries are frequently anticipated, the changes associated with laparoscopy are often more insidious. The pneumoperitoneum and reverse Trendelenburg positioning used in laparoscopic procedures may result in profound physiologic perturbations. Insufflation of the peritoneum is associated with increased arterial pressure, increased systemic vascular resistance, decreased venous return, and a decrease in cardiac output. Pneumoperitoneum may also cause bradycardia and hypotension, all of which are exacerbated by the reverse Trendelenburg positioning required for these procedures. Patients with depressed cardiac function are at particularly high risk for hemodynamic collapse with these maneuvers. Usually the hemodynamic instability can be corrected by releasing insufflation and returning the patient to the supine position. Administration of an anticholinergic agent (e.g., atropine intravenously) may be required if bradycardia is persistent.

Postoperative Management

Postoperatively the morbidly obese patient requires close monitoring for respiratory failure, hemodynamic instability, thromboembolism, and severe metabolic abnormalities. Unless significant cardiopulmonary disease is present preoperatively, most of these patients do not require postoperative admission to the ICU. Specialized bariatric nursing units are often well equipped and sufficiently experienced to monitor and provide appropriate postoperative care to the morbidly obese patient.

RESPIRATORY

Prior to extubation, placing patients in a reverse Trendelenburg position may help relieve increased abdominal pressure and facilitate diaphragmatic excursion during spontaneous respiration. Patients should be extubated once they are fully alert, have recovered neuromuscular function, can perform a head lift, and demonstrate adequate spontaneous respiratory effort.

Patients with respiratory insufficiency as a result of OHS or severe OSA may require prolonged postoperative ventilatory support. Weaning parameters should be aimed to restore preoperative blood gas levels. Following extubation, patients with OSA should have CPAP initiated in the recovery room and anytime the patient is not fully awake. Studies have demonstrated that early initiation of positive airway pressure (CPAP/BIPAP) postoperatively improves respiratory status and reduces the risk of respiratory failure. Continuous pulse oximetry and nasal capnography are often used to monitor oxygenation and ventilation in the early postoperative period. Use of incentive spirometry and maintenance of the head of the bed at least 30 degrees minimizes atelectasis and increase airway stability.

HEMODYNAMICS

The morbidly obese patient should be monitored postoperatively with continuous ECG telemetry. This is especially important in patients with OSA who are predisposed to serious cardiac

arrhythmias. Further cardiac evaluation should be performed per preoperative recommendations by the appropriate consultant and as indicated by the clinical status of the patient. Patients with significant cardiopulmonary disease should continue care in the ICU setting until hemodynamic parameters are stabilized.

VENOUS THROMBOEMBOLISM

Venous thromboembolic prophylaxis should be continued throughout the postoperative course. A multimodality approach with pharmacologic (e.g., unfractionated heparin or low-molecular-weight heparin) and nonpharmacologic therapies should be undertaken. Sequential compression stockings are recommended while the patient is at rest. Early ambulation should be encouraged unless specific surgical restrictions apply. A high index of suspicion must be present when evaluating for deep venous thrombosis (DVT). Subjective evaluation of extremities for edema or size discrepancy is often difficult, as such signs may be present preoperatively and in the absence of DVT. If venous thromboembolism is suspected, prompt evaluation is recommended and consideration should be given for immediate empiric therapeutic anticoagulation until the diagnosis has been confirmed or disproved.

ANALGESIA (see Chapter 87)

Postoperative analgesia requires careful consideration of pharmacokinetics in addition to the higher prevalence of airway obstruction in the morbidly obese. Because of excess fat stores, obese patients have a larger volume of distribution and prolonged storage of lipophilic drugs, such as fentanyl. Furthermore, to achieve a therapeutic level, higher initial doses may be required. In the case of lipophilic drugs, doses necessary to achieve the desired end point may persist, causing prolonged effects. Patient-controlled analgesia (PCA) without a basal rate is the recommended method of pain control. Use of lipophilic narcotics, such as fentanyl, should be avoided when possible and if used should be based on predicted body weight (see Tables of Predicted Body Weight in Appendix E). Similarly benzodiazepines should be used with caution as relaxation of pharyngeal musculature may cause airway obstruction.

Patients receiving opioid analgesia must be continually monitored and reassessed for signs of respiratory depression. Opioid antagonists should be readily available. Regimens that include nonsteroidal anti-inflammatory drugs (NSAIDs), such as ketorolac or intravenous ibuprofen, may reduce the need for narcotics.

Neuraxial anesthesia is an attractive option for pain control in these patients, as it may result in more rapid recovery of respiratory function. It is important that an anesthesiologist experienced with the anatomic and pharmacokinetic variations seen in this population performs these procedures.

FLUIDS/ELECTROLYTES/NUTRITION

Morbidly obese patients often have underappreciated insensible losses intraoperatively. As a result, these patients frequently present postoperatively with hypovolemia. Because overaggressive resuscitation may negatively influence cardiac and pulmonary function, it is generally recommended to target resuscitation parameters using predicted body weight (see Appendix E).

Electrolyte status in patients who remain NPO and who have experienced large fluid shifts should be monitored routinely with comprehensive chemistry panels. Electrolytes should be replaced as indicated with particular attention to potassium, magnesium, and phosphate.

Hyperglycemia is associated with poor wound healing, surgical site infection, and intravascular volume depletion (the latter due to hyperglycemic-induced osmotic diuresis). Although there is

no consensus on optimal blood glucose for these patients in the ICU, in general glucose levels should be maintained less than 180 mg/dL. Insulin-dependent diabetic patients who are NPO may require continued basal insulin, but blood sugar should be monitored frequently to avoid hypoglycemia. Sliding scale insulin regimens may promote appropriate blood glucose levels in both insulin dependent and non-insulin-dependent diabetic patients. Patients who have undergone bariatric surgery will require specialized attention with respect to resuming oral intake and diabetic medications.

COMPLICATIONS

The morbidly obese patient requires a high level of care with frequent assessments. Physical examination is often difficult and unreliable because of body habitus. Failure to recognize the early signs and symptoms of impending complications may result in serious morbidity and mortality.

Abdominal examination of the morbidly obese patient is frequently of little value. It is well accepted that symptoms of peritonitis may not be evident because of the large abdominal girth. This fact is particularly pertinent when examining morbidly obese patients after abdominal operations. Failure to detect intra-abdominal pathology may result in rapid deterioration of the patient and, if left untreated, possibly death. Careful attention to aberrations in vital signs—including persistent tachycardia, respiratory distress, fever, and decreased urine output—may suggest an impending or ongoing intra-abdominal catastrophe.

Obesity is an independent risk factor for surgical site complications (see Chapter 14). Necrosis of peri-incisional adipose tissue and the development of seromas increase the potential for a wound abscess. Morbidly obese patients are also at increased risk of wound dehiscence because of elevated abdominal pressure and excessive tension on the incision. Abdominal binders are frequently used to minimize the tension around the incision.

Conclusion

As the prevalence of obesity increases, a greater number of morbidly obese patients will receive surgical care. These patients are extremely complex and require a skilled multidisciplinary team in order to reduce morbidity and mortality.

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CHAPTER 94

Thoracic Surgical Patient

Arminder Jassar ■ Taine T.V. Pechet

This chapter focuses on the perioperative care of patients undergoing thoracic surgical procedures and emphasizes key issues surrounding the management of these patients in the intensive care unit (ICU).

Preoperative

The preoperative evaluation of patients undergoing lung or esophageal surgery is often complex, and the decision to operate is heavily influenced by comorbid conditions and the urgency of the procedure. Although a comprehensive discussion of this topic is beyond the scope of this chapter, important elements to consider in all patients undergoing thoracic surgery include optimal imaging; evaluation for metastatic disease; and evaluation of pulmonary function, cardiac risk stratification, and management of comorbid conditions.

It is imperative to emphasize to patients the importance of smoking cessation several weeks prior to surgery. Although the optimal time interval between smoking cessation and lung resection remains poorly defined, a minimum of 2 to 3 weeks is advised. Quitting tobacco closer to the date of surgery has been shown to invoke a hypersecretory response in the airways. Additionally, patients should be encouraged to start an exercise program when appropriate. This serves as the foundation for mobilization and exercise after discharge. In patients with evidence of reactive airway disease, bronchodilator therapy should be optimized while minimizing the use of systemic steroids. Finally, all medications should be carefully reviewed with specific attention to whether the patient takes antiplatelet or anticoagulation agents. If the patient requires ongoing anticoagulation, a plan for postoperative anticoagulation should be developed.

Intraoperative

Critical elements of care during the thoracic procedure include patient positioning, analgesia strategies, ventilator and acid-base management, fluid replacement, and extubation considerations. For most thoracic procedures epidural analgesia, typically placed prior to the induction of general anesthesia, is appropriate. If placement of an epidural catheter is anticipated, the American Society of Regional Anesthesia and Pain Medicine has made specific recommendations regarding anticoagulation surrounding the time of the procedure (Table 94.1). The narcotic sparing effects of epidural analgesia combined with the excellent pain coverage make epidural analgesia optimal for thoracic surgical procedures. When this is not an option, however, intercostal nerve blockade with long-acting local anesthetic agents or placement of extrapleural or paravertebral infusion catheters may be a viable alternative (Chapter 87).

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The positioning for thoracic surgical procedures can have profound implications on the conduct of the operation as well as the anesthetic management. Most pulmonary resections are conducted in the lateral decubitus position, and a beanbag or other support device can be used to maintain this position. During positioning, it is imperative to pay close attention to axillary and arm position to avoid injury to the brachial plexus or other peripheral nerves. Adequate intravenous access, typically without the requirement for central access or monitoring, is usually established prior to positioning. Radial arterial cannulation and bladder catheterization are also typically employed. As with any surgical procedure that is anticipated to last several hours, appropriate padding and cushioning to prevent rhabdomyolysis and skin breakdown are important.

Most thoracic procedures require the institution of single lung ventilation. Careful monitoring of airway pressures during the operation is critical to avoid barotrauma. The relationship between fluid management and barotrauma continues to be an active area of investigation, but barotrauma seems to predispose to capillary leak and the development of postoperative pulmonary edema. This is particularly important during lung resection or pneumonectomy. The development of postpneumonectomy pulmonary edema or acute respiratory distress syndrome (ARDS) in the remaining lung remains a vexing clinical problem that is mitigated by attention to these intraoperative factors.

TABLE 94.1 ■ **Management of Anticoagulant Agents with Neuraxial Anesthesia**

Anticoagulant	Recommended time to withhold prior to neuraxial procedure*	If restarting, recommended time to withhold after the neuraxial procedure*
Alteplase (TPA)—full dose for stroke, MI, etc.	10 days	10 days
Aspirin	Does not need to be withheld	Does not need to be withheld
Clopidogrel	7 days	2 hours
Dabigatran	7 days	24 hours (or 6 hours after pulling an epidural catheter until next dose, whichever is later)
LMWH	12–24 hours	6–8 hours (wait 2 hours after pulling an epidural catheter to administer next dose)
NSAIDs	Do not need to be withheld	Do not need to be withheld
UF heparin (intravenous)	2–4 hours	1 hour (same time for delay in restarting after pulling epidural catheter)
UF heparin 5000 U q12h (subcutaneous for VTE prophylaxis)	Does not need to be withheld	Does not need to be withheld (wait 2 hours after pulling an epidural catheter until next dose)
Warfarin	5 days (INR should be less than 1.5)	2 hours (wait until INR less than 1.5 before pulling epidural catheter)

*Recommendations made by the American Society of Regional Anesthesia and Pain Medicine.
UF, unfractionated; VTE, venous thromboembolism; LMWH, low-molecular-weight heparin; NSAIDs, nonsteroidal anti-inflammatory drugs; INR, international normalized ratio; TPA, tissue plasminogen activator.

Postoperative

These patients should generally be cared for in units where the nursing and ancillary staffs are familiar with the salient issues. Information that should be discussed during daily rounds includes vital signs, oxygenation, urine output, chest tube output, telemetry for arrhythmia detection, respiratory patterns and lung exam, status of air leaks, ambulation, and bowel function. The remainder of this chapter focuses on specific issues that are particularly relevant to the thoracic surgical patient in the postoperative period.

INITIATING ENTERAL FEEDING

Most patients who undergo pulmonary resection can eat the next day or, rarely, the same day of surgery. It is critical, however, to minimize the risk of aspiration. Aspiration is a common occurrence following thoracic surgery, in part related to laryngeal dysfunction resulting from double lumen endotracheal tube placement. One of the most effective methods to minimize aspiration is to ensure the patient is not in the recumbent or semirecumbent position while eating. Formal swallow evaluations have not been found effective when performed routinely on all patients, but informal supervision during the early phase of recovery to detect cough and to emphasize the importance of careful mastication and swallowing is helpful. Thin liquids are usually difficult for patients with a compromised larynx to swallow properly, and thickening agents or delayed introduction of thin liquids should be considered. Patients who have undergone esophageal procedures are at even higher risk of aspiration likely related to neurapraxia and muscle dysfunction from cervical dissection. In these patients, introduction of oral nutrition or medications is typically delayed

to permit esophageal anastomoses to heal. Hoarseness, often indicative of recurrent laryngeal nerve dysfunction, can also last for several days because of vocal cord edema.

FLUID AND ELECTROLYTE MANAGEMENT

Avoidance of hypervolemia is critical in patients undergoing thoracic surgical procedures. There are several mechanisms by which lung resection is thought to increase the risk of perioperative pulmonary edema. These include direct lung injury during intraoperative lung manipulation, disruption of lymphatic drainage by mediastinal lymphadenectomy, and alveolar hyperinflation (so-called volutrauma or ventilator-associated lung injury [VALI]) during single lung ventilation. Additionally, extensive lung resection decreases the total cross-sectional area of the pulmonary vasculature resulting in increased blood flow to the remaining lung, typically at higher pressure. This increased blood flow leads to increased pulmonary capillary pressures and increased transcapillary fluid flux caused by Starling forces. As a result, patients who undergo pneumonectomy are at especially high risk for postoperative respiratory decompensation, known as postpneumonectomy ARDS (despite being unilateral), and volume restriction is particularly important in these patients. Interestingly, studies that have evaluated the pleural fluid in patients with new effusions postoperatively have found the effluent to be exudative rather than transudative. This has led many to believe that the etiologies of effusion and edema are more complex than simply "fluid overload."

In general, most patients who are postoperative from thoracic surgery should be maintained on a low rate (0.5 mL/kg/h) of intravenous fluids. These can be discontinued once the patient is able to tolerate oral intake. A urine output of 0.5 mL/kg/h is usually acceptable. Diuresis should be augmented as tolerated to wean off supplemental oxygen.

ANALGESIA

Adequate pain control is essential not only for comfort but also for recovery. Poor pain control results in splinting, an inability to ambulate, and clear secretions, which can result in respiratory distress, pneumonia, and reintubation. Preoperative placement of epidural catheters for analgesic infusion (patient-controlled epidural analgesia [PCEA]—typically a local anesthetic such as bupivacaine and an opioid such as fentanyl) is the standard of care for most procedures (Chapter 87). Infusions through the PCEA are typically started prior to the conclusion of the operative procedure. The level of analgesia should be monitored frequently, and adequate pain control is essential. The epidural catheter can be maintained for up to a week if needed, but typically it is removed 2 to 4 days after surgery, following removal of the chest tube. In cases of malfunction or the inadvertent loss of the epidural catheter within the first 1 to 2 days after thoracotomy, immediate replacement by a pain specialist should be considered. In cases where the incision is very large and not able to be covered adequately by PCEA alone, an intravenous narcotic can be added and the epidural can be changed to local anesthetic only. Shoulder discomfort on the operative side is common, and intravenous (IV) or oral nonsteroidal agents (nonsteroidal anti-inflammatory drugs [NSAIDs]) such as IV ketorolac or IV ibuprofen can provide a useful adjunct; however, administration should be discussed with the surgical team given the risks of renal dysfunction and bleeding. Finally, topical application of a local anesthetic, such as a lidocaine patch, can be efficacious as well.

MANAGEMENT OF SECRETIONS

An aggressive approach to the management of secretions throughout the perioperative setting is critical to the successful recovery of patients undergoing both pulmonary and esophageal procedures. Pulmonary secretions predispose the patient to the development of mucous plugging, atelectasis, and pneumonia. The mortality for patients who develop pneumonia following

Electrolyte abnormalities are common in the perioperative setting. Hypokalemia should be aggressively corrected to reduce the risk of arrhythmias. Hyperkalemia should typically be treated first with diuretic administration. Hyponatremia, often from syndrome of inappropriate antidiuretic hormone (SIADH), is also common and should be treated with free water restriction, added dietary salt, and attention to other electrolyte abnormalities, particularly potassium (Chapters 39 and 84). Serum sodium concentrations in the 131 to 135 mEq/L range are common and can be managed without aggressive therapy.

ANTIBIOTICS

Antibiotics should be administered 30 to 60 minutes prior to incision and continued for 24 hours for most thoracic surgical procedures. Extended duration antibiotics are not recommended after elective pulmonary or esophageal resections. A rapid and aggressive approach to early detection and antimicrobial therapy for bronchitis, however, is advised. Patients who have undergone procedures for the management of empyema or pleural space infection should be treated initially with broad-spectrum antibiotics. The antimicrobial spectrum can then be tapered based on intraoperative culture data. A 6-week course of therapy is typically recommended for pleural or mediastinal contamination. Some surgeons advocate the use of prophylactic antibiotic coverage in patients with massive postoperative air leaks, but there are insufficient data to uniformly endorse this practice.

esophagectomy may be as high as 20%. Aggressive chest physiotherapy ("pulmonary toilet") prevents the accumulation of secretions in the tracheobronchial tree. Patients are encouraged to frequently cough, usually every 10 to 15 minutes, and should be instructed to properly use an incentive spirometer every hour while they are awake. Patients should begin ambulating on the day of the operation if possible. If the chest tubes require suction during ambulation, a number of portable suction systems are available. Thoracic walkers—which permit stabilization, oxygen administration, and chest tube drainage during ambulation—are also available. In patients with poor cough, aggressive chest physical therapy including percussion (manual or automated using vibrating vests) should be considered to help mobilize and clear secretions. Humidified nebulizer therapy, hypertonic saline solution, and *N*-acetylcysteine (both directly instilled intratracheally) can also be helpful. Bedside bronchoscopy, nasotracheal suctioning, and, occasionally, early tracheostomy may be required in patients who are unable to effectively clear secretions.

HEMODYNAMIC MANAGEMENT

Supplementation of vasoactive medications may be required to maintain an optimal perfusion pressure in patients with neuraxial blockade. Although the epidural primarily decreases blood pressure by increasing venous capacitance, excessive volume administration can be harmful in these patients. Alpha-adrenergic receptor agonists, such as phenylephrine, in moderate doses (25 to 75 mcg/min) are often utilized to avoid aggressive volume infusion. Systolic blood pressure monitoring may be superior to mean blood pressure measurements because many patients have a reduced diastolic blood pressure from the epidural-induced sympathectomy. In patients taking beta-blockers preoperatively, beta-blocker therapy should be reinstituted postoperatively as the blood pressure tolerates.

Supraventricular arrhythmia, particularly atrial fibrillation, is common following lung resection and occurs in 25% to 50% of such patients. The incidence increases with advanced age and the extent of lung resected. Electrolyte abnormalities (hypokalemia, hypomagnesemia), diuretic use, beta-blocker withdrawal, fluid shifts, and irritation of the pulmonary veins during the operation may all predispose to atrial dysrhythmias. All patients should have continuous telemetry monitoring postoperatively, but the duration may vary from 24 to 72 hours. Patients who have undergone a pneumonectomy are at a higher risk of arrhythmias, and they should be monitored more closely. In patients who develop an atrial tachydysrhythmia and remain hemodynamically stable, beta blockade or calcium channel blockade in incremental doses to establish rate control should be the initial therapy (Chapter 34). Chemical cardioversion is typically attempted if 24 hours of rate control with electrolyte repletion has failed.

MANAGEMENT OF CHEST TUBES

Chest drains are typically left in situ after pulmonary resections to facilitate removal of secretions and evacuation of air. The drainage/collection chamber should be routinely interrogated for the presence of an air leak (Chapter 35). A chest radiograph is typically obtained in the recovery area to assess the degree of lung expansion. The duration of chest drainage and the application of suction are often provider specific, but general recommendations include the use of water seal rather than suction, even in presence of an air leak. The gentle application of suction (e.g., negative 10 mm Hg) can be beneficial if it successfully achieves pleural apposition, but otherwise it will likely prolong and may worsen the air leak. Chest drains can be removed when the air leak ceases and the drainage decreases to less than 300 to 400 mL/24 hours (or < 100 mL/shift). The practice of draining a fresh pneumonectomy space is variable. Chest tubes in postpneumonectomy patients should never be connected to suction as that will result in ipsilateral mediastinal shift and hemodynamic collapse. Postpneumonectomy tubes should generally be removed on postoperative day

Many clinicians prefer to avoid amiodarone because of concern for pulmonary toxicity, which has been described in both chronic and acute settings. Others favor early administration of amiodarone, but for a limited period. Current data do not support the use of digitalis therapy in thoracic surgery. Electrical cardioversion should be considered if attempts to cardiovert pharmacologically have been unsuccessful or the patient becomes hemodynamically unstable. Administration of unfractionated heparin should be considered in patients with supraventricular arrhythmias lasting beyond 48 hours, but with attention to the risks of epidural and surgical site bleeding.

1 to minimize the risk of infection. These catheters can be removed at either maximal inspiration or maximal expiration to help adjust the mediastinal position. The chest cavity usually fills with fluid over the course of several weeks following a pneumonectomy; however, a rapid accumulation of fluid can sometimes result in compression of mediastinal structures and cardiac tamponade and should trigger concern for active hemorrhage or development of a chylothorax.

A requirement for prolonged chest drainage is one of the most common complications following pulmonary surgery. Air leaks occur as a result of visceral pleural injury during the operation but more frequently are due to the inability of the raw lung surfaces to heal or persistent tension on a parenchymal staple line. Dehiscence of the bronchial stump closure must always be considered, and, if suspected, bronchoscopy should be performed for direct inspection. As malnutrition is one of the greatest risk factors for bronchial dehiscence, aggressive and early nutrition is essential in these patients (Chapters 15 and 16). If possible, steroids should be avoided (or minimized) to promote wound healing. When continued mechanical ventilation is required postoperatively, positive pressure ventilation should be administered at the lowest possible pressure settings. It is often helpful to use a pressure-cycled mode of ventilation to minimize the risk of barotrauma at parenchymal staple lines and regions of bronchial stump closures.

OXYGEN TITRATION

Postoperative oxygen requirements are common following thoracic surgery. Supplemental oxygen requirements can usually be diminished to 2 to 3 L/min administered by nasal cannula within hours of surgery. High-flow supplemental oxygen should be humidified to minimize nasal and airway desiccation and concretion of secretions. Diuretic therapy and efforts to maximize lung expansion and minimize atelectasis are the principal interventions available to wean the patient off of oxygen prior to hospital discharge.

SPECIFIC ISSUES SURROUNDING THE CARE OF ESOPHAGECTOMY PATIENTS

There are fundamental differences in the postoperative care of patients who have undergone esophagectomy compared with that of patients who have undergone pulmonary resection. After esophagectomy, the gastrointestinal continuity is maintained by either a gastric pull-through or a colonic or small bowel interposition. Unfortunately, the viability of the conduit often depends on a tenuous blood supply; hence, all efforts should be instituted to avoid periods of hypotension or the initiation of vasoconstrictor therapy. Efforts must be directed to maximize perfusion of the conduit vessel. Conduit necrosis is a serious problem that may require reoperation and temporary gastrointestinal discontinuity. If the region of necrosis is large, it can be fatal. Patients who have undergone esophagectomy do not have the same restriction on volume resuscitation as the lung resection patients, and fluids should be infused as needed to maintain adequate perfusion. Fever, persistent tachycardia, the presence of new effusions, or a change in mental status are all harbingers of serious problems (e.g., sepsis) and must be promptly evaluated. In the case of respiratory distress, the need for reintubation should be continuously assessed, and an emergent intubation should be preempted by intubating the patient in a semielective fashion. These patients should be intubated by an experienced practitioner, preferably under fiberoptic guidance to minimize the risk of esophageal intubation or undue stretch on the cervical anastomosis with laryngoscopy. Postoperative pain control remains of paramount importance (Chapter 87). Measures should be taken to prevent aspiration, as the normal mechanisms of swallowing and prevention of reflux are compromised because of the absence of the lower esophageal sphincter and pressure changes resulting from an intrathoracic stomach. The addition of pyloroplasty to the procedure can also increase risk of bile reflux. All of these patients will have a nasogastric tube placed at the time of

Management options for ongoing parenchymal air leaks include continued drainage (which does not preclude discharging the patient home with a chest tube), chemical pleurodesis, and transposition of a muscle flap. Chemical pleurodesis is rarely effective without the apposition of the parietal and visceral pleural surfaces. Talc powder should be avoided as a sclerotic agent in the setting of a prolonged air leak because of the risk of chronic infection by a foreign body in an infected space. The preferred agent in such an instance is doxycycline. Rarely, a blood patch can also be administered by instilling 50 to 100 mL of the patient's blood into the chest cavity.

operation. Importantly, this tube should not be manipulated and must be checked frequently to ensure proper function. If suctioning is compromised, the tube can usually be flushed with small aliquots of water or saline to remove any obstruction. Oral intake is strictly prohibited in these patients during early recovery. The timing and method of evaluation of anastomotic integrity vary widely but generally occur 5 to 8 days following surgery. Typically, a feeding jejunostomy tube is also placed during the initial surgery, and enteral feeds should be initiated once bowel function resumes.

Conclusion

The perioperative management of patients undergoing thoracic surgical procedures spans a range of disciplines and requires significant attention to detail. Hemodynamic lability and arrhythmias are common in the postoperative period. Great care and specific techniques may be required to maximize the clearance of airway secretions. Patients following esophagectomy and esophageal replacement require a specific focus directed at maximizing conduit perfusion while minimizing respiratory complications.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 95

Approach to the Trauma Patient

Steven R. Allen ■ Carrie A. Sims

Trauma is the leading cause of death in people under the age of 45 and represents a significant public health problem in the United States. In addition to the profound effect on public health, the implications from traumatic injuries consume a substantial amount of medical and economic resources. Medical expenditures attributed to injury exceeded $117 billion in 2000 with nearly 10% of total U.S. medical spending going toward the care and rehabilitation of the injured patients.

Patterns of Mortality from Trauma

In 1983 Donald Trunkey described, in what has now become a classic paper in trauma literature, the trimodal distribution of trauma deaths. The first time period occurred within 1 to 2 hours of the injury and was defined as "immediate." The lethal injuries in this "immediate" period were usually due to lacerations of the brain stem, spinal cord, heart, aorta, or other large blood vessels and accounted for 45% of all trauma deaths. "Early" deaths (Trunkey's second time period) were those that occurred within 4 hours of injury. Thirty-four percent of deaths occurred in this time period and were due to subdural and epidural hematomas, tension hemo- or pneumothoraces, splenic rupture, liver lacerations, pelvic fractures, or multiple injuries with major blood loss. Injuries occurring in this time period were found to benefit most from expeditious interventions such as decompressive craniectomy, tube thoracostomy or splenectomy. The third peak, termed "late deaths," occurred days to weeks after the injury and accounted for 20% of all trauma-related mortality. These deaths were secondary to infection, the acute respiratory distress syndrome (ARDS), and multiple organ system failure (MOSF). Since this description of trimodal trauma-related mortality, there have been significant advances in injury and safety prevention as well as the development of regionalized trauma systems and implementation of rapid prehospital transportation networks. As a result of these developments and further maturation of trauma systems, more recent reports question the validity of the classical trimodal mortality model.

The development of the current Advanced Trauma Life Support (ATLS) has also had a significant impact on trauma-related mortality. Injuries are addressed in a systematic fashion (the classic "ABCs" of resuscitation) such that the *airway* is secured first, followed by treatments to improve *breathing* (e.g., decompression of a pneumothorax), and finally *circulation* is restored by cessation of hemorrhage and fluid resuscitation.

Initial Management of the Trauma Patient

The *primary survey* (Table 95.1) is used to quickly identify and treat life-threatening injuries and includes securing the airway, assuring adequate ventilation and oxygenation, and resuscitating with intravenous fluids. Fluid resuscitation is initiated with crystalloid, preferably 0.9% normal saline, or blood products. Transfusing packed red blood cells (pRBCs) in the face of active

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The ATLS system was originally founded after the pilot of a crashed airplane, Dr. James Styner (also an orthopedic surgeon), witnessed firsthand the flawed "system" of trauma care that existed in the 1970s. Based on this experience, he and others revolutionized the initial treatment of the injured patient by developing a standardized, systematic approach to the initial assessment.

In 1978, the first ATLS course incorporating these initial ABC's of patient management was taught, and in 1979 the course was formally adopted by the American College of Surgeons, Committee on Trauma. It is now taught throughout the United States and in 46 other countries. ATLS gives practitioners a standardized, systematic approach to the injured patient. These advancements in pre-hospital care have led to the timely delivery of patients with life-threatening injuries to emergency departments within the "golden hour" and have saved many of their lives as a result of the rapid assessment and treatment set forth by the ATLS guidelines.

hemorrhage is traditionally preferred because it not only restores intravascular volume but also improves the oxygen-carrying capacity (see Chapters 9 and 19 for more details about recommendations for the transfusion of blood products).

Following the primary survey, the patient is examined from head to toe in a detailed yet expeditious fashion in order to identify other injuries. This comprises the *secondary survey*. Adjuncts to the secondary survey include radiographs, ultrasound, and computed tomography.

The ATLS course recommends obtaining an anterior-posterior (AP) chest radiograph and a pelvic film. The chest radiograph is an excellent way to identify pneumothoraces, hemothoraces, rib fractures, and, if intubated, the position of the endotracheal tube. The pelvis radiograph is strongly indicated if the patient is unable to be examined because of obtundation or sedation, has a pelvic deformity, is experiencing pain, or is hemodynamically unstable.

Focused abdominal sonography for trauma (FAST) is a commonly used diagnostic tool to evaluate blunt abdominal trauma. The sensitivity and specificity of this modality range between 73% to 88% and 98% to 100%, respectively. FAST has several advantages over other imaging modalities. It is rapid (usually performed in a matter of minutes), non-invasive, and easily performed in the trauma bay in concert with the ongoing resuscitation. Ultrasound machines are also portable and allow the study to be repeated easily whether the patient remains in the trauma bay or is moved to the intensive care unit (ICU). The FAST is helpful in identifying intra-abdominal hemorrhage and in helping to triage the unstable patient with multiple injuries. It can also be used to triage the pregnant patient, thereby limiting the amount of radiation exposure to the fetus.

Other imaging, which may be indicated in the stable patient, includes computed tomography (CT) scans of the head, c-spine, chest, abdomen, and pelvis. CT scans of the head without contrast are essential for identifying intracranial injuries that may require neurosurgical intervention such as subarachnoid, subdural, and epidural hemorrhages. A CT scan of the cervical spine, also without contrast, allows excellent visualization of bony abnormalities, malalignment of vertebrae, or vertebral retropulsion into the spinal canal. These images may be reconstructed in sagittal and coronal dimensions in addition to the standard axial planes. Although CT scans of the cervical spine are very sensitive for fractures and malalignment, they are not adequate to diagnose ligamentous injury.

CT scans of the chest, abdomen, and pelvis will identify great vessel injuries, pulmonary contusions, pneumothoraces, solid organ injuries to the spleen, liver, and kidneys, as well as free fluid suggestive of hollow viscous injuries. However, a CT scan of the abdomen and pelvis immediately after the injury is unable to reliably diagnose hollow viscous or pancreatic injuries as there may be no or minimal free fluid within the abdomen. To make this diagnosis, one must rely on physical exam and clinical suspicion.

It must be emphasized that hemodynamically unstable patients who have sustained an injury via a blunt mechanism should not be evaluated by CT. Rather, they should undergo FAST exam or diagnostic peritoneal lavage (DPL) and, if appropriate, they should be taken to the operating room for surgical exploration.

TABLE 95.1 ■ **The ABCs of the Primary Survey**

The ABCs	Specific Area Surveyed
A	Airway maintenance with cervical spine control
B	Breathing and ventilation
C	Circulation with hemorrhage control
D	Disability: check neurologic status
E	Exposure: completely undress patient

Prior to the widespread utilization of computed tomography, a lateral cervical spine radiograph was done to identify malalignment of neck vertebrae. This was routinely followed with an anterior cervical and odontoid view to complete the evaluation.

One drawback to the FAST exam is that it is user dependent. With experience, however, an operator may detect as little as 200 mL of intra-abdominal fluid. Additionally, the FAST exam is less reliable at identifying injuries not typically associated with a large amount of intra-abdominal fluid early in their presentation (e.g., hollow viscous, pancreatic injury, retroperitoneal injuries). However, the FAST is an excellent tool for helping to triage patients with blunt mechanisms. Unstable patients with a positive FAST require emergent laparotomy, whereas stable patients with a positive FAST may be assessed with other imaging modalities including computed tomography scans to better evaluate the extent of their injuries.

Patients with multiple injuries frequently require specialized care. Patients with traumatic brain injuries, for example, may require intracranial pressure monitoring and associated treatment (see Chapters 41 and 99). Those with chest trauma may require mechanical ventilator support (see Chapter 100), whereas patients with solid organ injuries or pelvic fractures may need aggressive fluid resuscitation and hemodynamic monitoring. These treatment modalities and procedures are best served in the surgical intensive care unit (SICU).

EVALUATION OF THE TRAUMA PATIENT UPON ARRIVAL TO THE INTENSIVE CARE UNIT

Upon arrival to the SICU, the trauma patient should undergo another complete evaluation by the critical care team. The details of the patient's trauma event and clinical condition should be reviewed and a detailed account of any performed procedures should be communicated. Past medical history including medications, allergies, and social habits must be obtained, often from the patient's family members and friends. A complete physical exam must be performed. All laboratory tests should be reviewed in detail and additional tests should be obtained as necessary such as lactate, arterial blood gases, hemoglobin, and creatine phosphokinase (CPK). The trends of these values is often more important than a single measurement. The ICU physician should reexamine all previously obtained radiographs, including CT scans, to look for injuries that may have been missed. It is helpful to make a list of all lab tests and radiographs that remain outstanding or need an official interpretation by a radiologist to ensure that nothing is missed (Box 95.1).

Although it is not uncommon for new injuries to be found over the ensuing days following an accident, the goal is to identify these injuries in an expeditious manner. Patients who are unconscious are at particularly high risk for missed injuries including extremity, hand, foot, and facial bone fractures. Injuries that may present in a delayed fashion include hollow viscous and pancreatic injuries. Additionally, subdural hematomas may develop subsequent to the initial scan. Complications from the initial injury such as compartment syndrome of the extremities and the abdomen must be anticipated and, if identified, treated rapidly in order to minimize residual damage and dysfunction (see Chapter 98).

BOX 95.1 ■ Trauma Patient Evaluation upon Arrival to the Intensive Care Unit

History

Obtain a history of the injurious event.
Review prior hospital course and anesthesia record.
Obtain past medical history from family and friends.

Physical Examination

Perform a physical examination.

Laboratory and Radiographic Tests

Review all laboratory tests and make an inventory of outstanding results.
Review and inventory all radiographs and CT scans.
List all radiographs that are outstanding or need to be repeated.
List all radiographs without official interpretation, and review them with the radiologist.

Ongoing Therapies

Survey the patient's current status, medications, and treatments.

List of All Known and Potential Injuries

List all *known and evaluated* injuries with a treatment plan.
List all *known and partially evaluated* or unevaluated injuries with a time line for evaluation.
List all *potential* injuries with a surveillance plan to diagnose them.

Coordination and Consultation

Designate a single coordinating physician.
Obtain appropriate consultations.

Immediate Postoperative Priorities

In the immediate postoperative period, the management priorities of the trauma patient are similar to those of other critically ill postoperative patients. The patient may require immediate resuscitation with crystalloid solutions such as 0.9% saline or lactated Ringer's. If blood loss was excessive in the operating room or if the patient has developed a coagulopathy, blood or fresh frozen plasma should be given. The adequacy of resuscitation may be assessed and followed by several means (see Chapter 7). Echocardiography may also help to guide resuscitation, as one may assess volume status in real time by measuring the size of the right and left ventricles, the ejection fraction, and the degree of inferior vena cava collapse during inspiration. End points of resuscitation must be continually reassessed. If mean arterial pressure remains less than 60 to 65 mm Hg, despite appropriate intravascular volume, vasoactive medications should be considered.

Secondary Complications

Trauma patients, like all critically ill patients, are at risk of developing ongoing complications throughout their hospital stay. Limited mechanical ventilation with early extubation is desirable and will reduce the risk of ventilator-associated pneumonia. Patients should be vigilantly monitored for infectious complications such as pneumonia and urinary tract or bloodstream infections and treated early with appropriate antibiotics (see Chapter 14).

Early nutritional support is paramount in the trauma patient. Trauma patients become extremely catabolic after injury and require increased nutritional support. Enteral nutrition is preferable, however, total parenteral nutrition (TPN) may be required if the gastrointestinal tract is injured or not otherwise functional. Because TPN is associated with an increased risk of infectious complications, biliary stasis, acalculous cholecystitis, and atrophy of the intestinal mucosa, enteral nutrition is the preferred mode of nutritional support unless otherwise contraindicated (see Chapters 15 and 16).

BOX 95.2 ■ Intensive Care Unit Management Pearls for Trauma Patients

Airway and Breathing

Formulate a plan for weaning patients from ventilatory support.

Circulation

Ensure adequate cardiac function.
Correct acidosis.
Ensure that all organs are adequately perfused.
Wean inotropic support.
Minimize the amount of fluids administered.
Maximally concentrate medications.

Diagnosis and Treatment

Control ongoing bleeding or coagulopathy.
Diagnose and treat other injuries.
Perform early operative fixation of fractures.
Avoid prophylactic antibiotic administration.
Monitor for infections.

Nutrition

Start nutrition early.

Disposition

Consult discharge planner early.

Other complications that trauma patients are at particularly high risk for include deep venous thromboses (DVT) and subsequent pulmonary emboli (PE). Early fracture fixation and mobilization of the trauma patient along with adequate pharmacologic DVT prophylaxis are necessary to reduce the risk of these complications (Box 95.2). Risk factors for venous thromboembolism in trauma patients have been studied and include (1) spinal cord injury with paraplegia or quadriplegia, (2) severe closed head injury with a Glasgow Coma Score < 8, (3) age ≥ 40 years, (4) pelvic fracture, (5) lower extremity fracture, (6) receiving mechanical ventilation for greater than 3 days, (7) venous injury, (8) shock (systolic BP < 90 mm Hg) on admission, and (9) major surgical procedure.

Although unfractionated heparin (UH) (5000 units two to three times per day) can be used, low-molecular-weight heparin (LMWH) has been shown to decrease the incidence of DVT so that many trauma centers consider use of LMWH to be the standard pharmacologic prophylaxis for trauma patients. Because LMWH is associated with more bleeding complications than PCDs, its use cannot be recommended initially in patients with intracranial hemorrhage, ocular injuries, or splenic or liver lacerations. In addition, patients who require an epidural catheter should not receive LMWH due to an increased risk of epidural hematoma.

Conclusion

Management of the critically ill trauma patient requires a systematic approach to ensure that all injuries are identified and managed appropriately. The patient must be reassessed frequently in the emergency department (trauma bay) or ICU, and resuscitation must be continued until the end points of resuscitation are met. In addition to addressing the patient's known injuries, the ICU team must be able to recognize missed injuries and be ready to treat all potential secondary complications. The multiply injured trauma patient may have competing priorities and require the care of several different specialists. To control the occasional conflicting desires of the different consulting services, the ICU team should have the primary responsibility for the patient's care in the ICU and should coordinate the patient's overall care including all treatment plans, procedures, and operative interventions.

An annotated bibliography can be found at www.expertconsult.com.

For example, a 1996 study by Knudson et al reported an incidence of 0.8% for DVT in patients given LMWH compared to a predicted incidence of 9.1%. Incidence of DVTs in the LMWH group also was significantly lower than the DVT incidence of 2.5% for those who received only sequential pneumatic compression devices (PCDs).

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CHAPTER 96

Critical Care for the Orthopedic Patient

Samir Mehta

Although orthopedic patients with isolated extremity injuries or those undergoing elective procedures rarely require care within an intensive care unit (ICU), patients who have sustained multisystem injuries sustained by high-energy impacts or pelvic ring injuries generally require ICU-level care. The sequelae of these injuries can be widespread including, but not limited to, hypotensive shock, sepsis, acute respiratory distress syndrome (ARDS), pulmonary embolism, fat embolism, acute renal failure (ARF), acidosis, and death. This chapter introduces some of the unique aspects of care required for the musculoskeletal polytrauma patient. In addition, it describes musculoskeletal injuries of the extremities and pelvis, including their associated orthopedic procedures.

Approach to the Patient with Multiple Orthopedic Injuries

All trauma patients should be first evaluated and treated in accordance with the Advanced Trauma Life Support (ATLS) protocol outlined by the American College of Surgeons (see Chapter 95). Of note, patients with fractures of the acetabulum, pelvis, or femur may require a large resuscitation upon presentation. Following the initial resuscitation, all patients should undergo a secondary survey of all organ systems, including the musculoskeletal system. The musculoskeletal survey consists of a head-to-toe, systematic examination that begins with observation. The long bones, axial skeleton (spine, clavicle, pelvis), and joints should be palpated with adequate assessment and documentation of neurologic and vascular function. Range of motion of all major joints should be assessed to detect instability or limitations of motion. In addition, the presence of swelling, ecchymosis, crepitus, visible deformity, and pain will guide further intervention.

As part of the initial assessment, a radiographic trauma series can be performed that includes the lateral cervical spine, anteroposterior (AP) chest, and AP pelvis radiographs. In addition, two orthogonal radiographs should be obtained at regions identified from the secondary musculoskeletal survey as potentially injured. In such cases, imaging should include the joint proximal and distal to the region of interest. Increasingly, trauma centers are utilizing comprehensive computed tomography (CT) scans as they have been shown to be more sensitive than traditional radiographic and clinical examinations

Despite a thorough initial musculoskeletal survey, it is possible for injuries to be overlooked, particularly in the polytrauma or critically ill patient. Intensivists should be aware of this possibility and assess for injuries that may have not been detected upon presentation (e.g., developing ecchymoses over a fracture site). In the polytrauma patient, the rate of missed musculoskeletal injuries can be as high as 25%.

There has been an increased appreciation of the systemic impact that orthopedic injuries have on morbidity and mortality in the polytrauma patient. Much of this work has focused on

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understanding the outcomes associated with early total care (ETC) versus damage control orthopedics (DCO). The latter appears to be superior and involves the staged management and stabilization of the injuries in order to minimize the complications associated with the "second hit" (physiologic overload after acute trauma as a result of operative interventions) (Figure 96.E1). As a result, an increasing number of patients with multiple orthopedic injuries are managed in the ICU for physiologic stabilization prior to definitive management. In contrast to thoracic and abdominal trauma, few orthopedic injuries require immediate surgical management before medical stabilization and optimization. Although not always visible, the energy that is required to induce a fracture can also significantly injure the surrounding tissue envelope. Such compromised soft tissue is not favorable for surgical intervention and can lead to sequelae such as infection, necrosis, or amputation. However, even patients who are felt to be too unstable for definitive fixation still require stabilization of their long bone injuries, compression of pelvic ring injuries, and reductions of dislocations despite their physiologic status.

Orthopedic Terminology

Knowing the fundamental nomenclature and vocabulary of orthopedics can facilitate greater understanding of the extent of injury as well as help effectively communicate to other physicians involved in the care of the patient.

The fracture location is generally described as diaphyseal (the shaft or mid-portion), metaphyseal (in between the mid-portion and joint), or intra-articular (within the joint). The fracture pattern is described as *transverse*, *oblique* or *spiral*, and *simple* or *comminuted*. The location and pattern of a fracture can help discern the particular mechanism of injury. Long bone fractures occur when energy imparted to the extremities cannot be dissipated in the soft tissues. Comminuted fractures are more apt to occur through higher energy mechanisms (such as a motorcycle collision) and may be more frequently associated with soft-tissue injury and exposed bone (i.e., open fracture). The type and rate of stress loading determine the fracture pattern. Slow torque typically causes a spiral fracture, whereas a high-energy direct blow will result in a comminuted fracture.

Closed Fractures

Fractures without soft-tissue injury such that the bone is not exposed are termed *closed fractures*. Fractures with a superficial laceration or abrasion near or at the fracture site are still considered to be *closed*. An intact soft-tissue envelope is associated with improved outcomes. Most closed fractures do not require immediate surgical fixation and can be temporized using external fixation, traction, or splints. However, delayed treatment of long bone injuries (e.g., femoral shaft fracture) or hip fractures, particularly in the elderly population, is associated with poor outcomes. Similarly, patients with soft-tissue compromise (i.e., a bone fragment tenting the skin) or progressive neurovascular compromise (i.e., worsening sciatic nerve function after a hip dislocation) should also be brought to the operating room (OR) on an urgent basis to prevent permanent damage.

Open Fractures

Fractures with soft-tissue injuries allowing the bone to communicate with the environment are termed *open fractures.* Open fractures are often associated with high-energy mechanisms or penetrating trauma. These fractures have an increased rate of complications due to soft-tissue disruption and colonization of bacterial flora within the wound. In addition to the general strategies utilized for closed fracture care, open fractures are often taken to the OR on an emergent basis to help prevent infection.

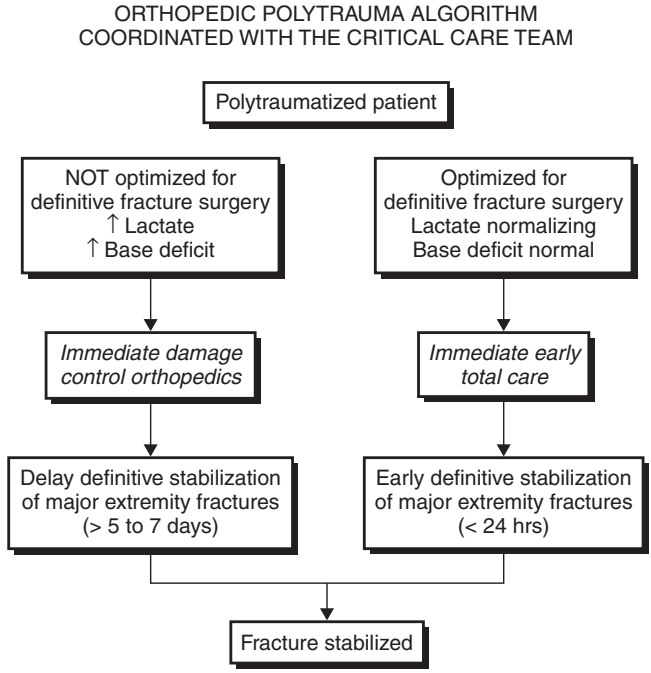


Figure 96.E1 Algorithmic care of the polytrauma orthopedic patient.

Dislocations

When sufficient translational, rotational, or distractive forces are exerted across a joint, the surrounding soft tissues, including ligamentous and tendinous structures, may become compromised. This can result in a dramatic disruption of the articular congruity of the joint, termed traumatic *dislocation* (Figure 96.E2). Dislocations sustained from higher energy mechanisms are more prone to neurovascular injury, avascular necrosis, and posttraumatic arthritis. Such dislocations need to be reduced emergently by the orthopedic surgeon. Patients with unstable dislocations may require splinting or external fixation.

In patients who have had a dislocation reduced, it is imperative that the associated neurovascular status be monitored at least every 2 hours for the first 24 hours to detect further neurovascular damage should the joint spontaneously dislocate. High-energy dislocations are especially prone to neurovascular injury with up to 50% of high-energy knee dislocations associated with neurovascular injury of the popliteal structures.

Dislocation of the hip manifests symptomatically as pain and shortening. Depending on the direction of the dislocation, examination of the injured limb will reveal persistent rotation, flexion/extension, or an abduction/adduction deformity. Dislocations associated with acetabular fractures have the worst prognosis. Patients presenting to the ICU after having been reduced will often have some form of traction or abduction pillow present to help stabilize the limb. Flexion, internal rotation, and adduction should be avoided. Keeping the limb in its reduced position is critical to maintaining joint congruity. Dislocation of the hip can result in sciatic nerve palsy or avascular necrosis of the femoral head. When such an injury is present, the neurovascular status and the limb alignment should be assessed frequently.

Elbow dislocations usually occur as a result of falling on an outstretched forearm. Patients may need operative treatment for grossly unstable elbow fractures. Prior to operative intervention the elbow should be held in a splint or sling in pronation. Shoulder dislocations often require patients to be completely immobilized in a brace for up to 3 weeks following injury. As with all dislocations, the patient's neurovascular status should be monitored and documented regularly.

Orthopedic Care and the ICU

OPEN FRACTURE CARE

The hallmark of open fracture treatment is preventing infection and maintaining the soft-tissue envelope. Open fractures require emergent surgical debridement for the removal of nonviable tissue and irrigation for decontamination of viable tissue. Debridement and irrigation should be performed within 6 hours from the time of injury. Other priorities in the immediate period include tetanus prophylaxis, intravenous (IV) antibiotics (e.g., generally a cephalosporin with or without an aminoglycoside), clean dressing for the wound, and removal of gross contamination. These efforts are vital for preventing loss of limb, osteomyelitis, gangrene, and sepsis.

Prophylactic antibiotic treatment is guided by the type of open fracture (Table 96.1). Open fracture typing is based on the degree of soft-tissue involvement and the energy of the injury. The degree and type of contamination must also be considered

Intravenous antibiotic treatment should continue for 48 hours after repair of an open fracture. Intraoperative culture results should be sought and modifications of antibiotics should be made accordingly. If there is a substantial degree of contamination or there is insufficient soft-tissue coverage, the patient should be expected to be taken back to the OR by the orthopedic team several times for repeat debridement and irrigation. Immediate postoperative management involves surveillance of the wound for evidence of infection and gangrene as well as delivery of antibiotics for an additional 48 hours after each OR visit.



Figure 96.E2 A lateral radiograph shows anterior dislocation of the tibia relative to the femur. The patient had an associated popliteal artery requiring immediate external fixation and vascular repair.

Patients with unreduced dislocations and concomitant head injury are at an extremely high risk for *heterotopic ossification*. This excess bone formation can complicate outcomes as patients improve from their head injury. It is imperative that patients who have a traumatic brain injury be closely assessed for dislocations, particularly of the elbow, hip, and shoulder, to limit further long-term disability. Heterotopic ossification can lead to limitation in joint mobility, contractures, and problems with hygiene, soft-tissue breakdown, and neurologic complications. If severe, patients may require an amputation.

TABLE 96.1 ■ **Gustilo-Anderson Classification of Open Fractures**

Type	Soft Tissue	Description	Antibiotics
I	Minimal	Low-energy mechanism	First-generation cephalosporin
	< 1 cm wound	Relatively "clean" wound bed	
II	1–10 cm	Low-energy mechanism	First-generation cephalosporin
		Moderate contamination of wound bed	
		Low-velocity gunshot wound (GSW)	
All III		High-energy mechanism*	
IIIa	> 10 cm		First-generation cephalosporin with an aminoglycoside
IIIb	> 10 cm	Contaminated; need for free tissue transfer (flap) to address soft-tissue defect	First-generation cephalosporin with an aminoglycoside
IIIc	> 10 cm	Vascular repair required	First-generation cephalosporin with an aminoglycoside†

*Includes segmental fracture, high-velocity GSW, or highly contaminated or crush injury.
†Add penicillin if significant contamination is seen or suspected. Vancomycin or clindamycin may be substituted in the case of penicillin allergy.
Data from Zalavras CG, Patzakis MJ. Open fractures: evaluation and management. J Am Acad Ortho Surg 2003; 11:212-219.

Patients may also receive a free tissue transfer/flap for coverage of the soft-tissue defect caused by the trauma (Figure 96.E3). This procedure is typically done by the orthoplastic surgery team and involves intricate microsurgery of blood vessels or neurologic structures. In most cases the goal is to "fix and flap" within 7 days of the injury, as this has been shown to limit the risk of osteomyelitis and promote bone healing. Typically, after free tissue transfer, patients require 5 days of observation in an ICU in order to receive frequent monitoring of the vascularity of the flap. In-dwelling Doppler probes, frequent neurovascular checks, and direct flap observation are all methods used to monitor the integrity of the free tissue transfer (Chapters 91 and 92). Early recognition of a flap that has lost its inflow or clotted off its outflow can be the difference between limb salvage and limb amputation.

METHODS OF FIXATION

Orthopedic surgeons utilize a variety of methods to temporarily stabilize and definitively treat patients: splints, casts, external fixation, traction, and open reduction and internal fixation (ORIF). Stabilization methods are utilized in the context of *damage control orthopedics* as well as aiding in pain control and mobilization.

Postoperative Concerns

OCCULT BLOOD LOSS

Although patients may receive proper resuscitation for the insults incurred as a result of the acute trauma, patients with extremity trauma often require additional and ongoing resuscitation for evident and occult blood loss (Table 96.2).



Figure 96.E3 A free-tissue transfer for the soft-tissue defect.

Splints are used to stabilize and immobilize a fracture site prior to more definitive management. Splints are constructed from a variety of materials such as plaster and are molded individually to fit the patient. Depending on the construction, it is often essential that the splint not get wet. Splints can be modified to allow access to the affected limb in order to conduct neurovascular checks and assess for progression of soft-tissue injury.

Casts are a more permanent form of splint and are usually applied after the soft-tissue swelling around a fracture site has subsided. Casts are designed to help maintain alignment of a fracture. As with splints, they should not be exposed to wetness and should remain clean. Complications from casting include cast burns and compartment syndromes. Both complications are more likely to occur in the unconscious or insensate patient who is unable to complain of pain. Patients should be encouraged not to scratch or otherwise manipulate a cast. Patients who arrive to an ICU setting from an outside hospital or an injury scene with a cast should have their cast removed by the orthopedic surgeon in order to assess the extent of their soft-tissue injury and neurovascular status.

External fixation is a percutaneous stabilization technique (Figure 96.E4) that allows rapid stabilization of a fracture. This technique also avoids the implantation of hardware at a site that is at risk for bacterial colonization and infection. Finally, external fixation facilitates wound care and patient mobilization. It can be used as a definitive treatment modality or as a method of temporization prior to more definitive management. Pin sites should be thoroughly cleaned on a daily basis using a topical antibacterial solution such as hydrogen peroxide.

Traction is often added to splints or external fixation devices and involves the application of longitudinal stabilization forces using a pin or wire through bone distal to the fracture site. Although in the past traction was used as a definitive method of treatment, it has been shown to be more beneficial if used only as a temporizing treatment until definitive stabilization can be completed.

Open reduction and internal fixation (ORIF) has been advocated in the patient with multiple injuries because it permits direct reduction of the fracture, early motion of joints, and patient mobilization. The latter improves pulmonary function, decreases the risk of infection, and reduces the risk of deep venous thrombosis. Stabilization of isolated long bone fractures within 48 hours is associated with reduced mortality, shorter ICU and hospital stays, and lower costs. A disadvantage of internal fixation is the requirement for surgery, with additional tissue trauma and blood loss. Internal fixation with intramedullary rodding may increase the risk for fat embolism syndrome and posttraumatic acute respiratory distress syndrome (ARDS), particularly in patients with

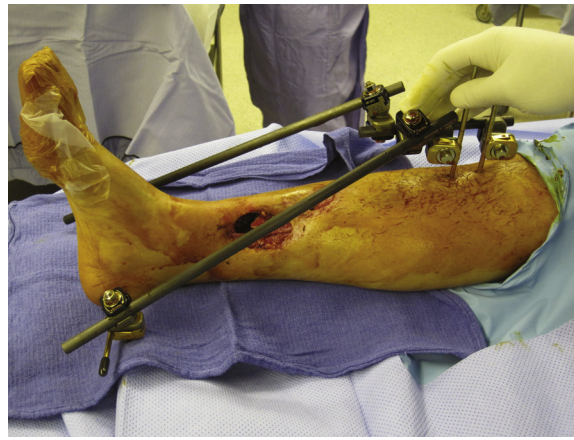


Figure 96.E4 Clinical photograph of an open type IIIB tibial shaft fracture with bone loss treated in a staged fashion. External fixation was applied until definitive fixation (including free tissue transfer) could be performed. Note that the external fixator pins are away from the zone of injury, planned surgical incisions, and necessary definitive hardware.

preexisting pulmonary injury. Surgical site dressings should be changed 48 hours after the operative procedure. Serosanguineous discharge from the wound is considered normal and is a result of bleeding and secretion of edematous fluids from the surrounding soft tissue. Hemovac drains will sometimes be placed intraoperatively to help monitor the volume of these fluids postoperatively. Excessive daily output (> 1 L) 48 hours postoperatively is concerning and should prompt consideration for reexploration. Purulent drainage from the wound or sutures is a significant concern and the treating surgeon should be notified immediately if this is identified.

TABLE 96.2 ■ **Estimated Occult Blood Loss in Acute Fractures**

Location of Fracture	Blood Loss (Units)
Ankle	0.5 to 1.5
Elbow	0.5 to 1.5
Femur	1 to 2
Forearm	0.5 to 1
Hip	1.5 to 2.5
Humerus	1 to 2
Knee	1 to 1.5
Pelvis	1.5 to 4.5
Tibia	0.5 to 1.5

COMPARTMENT SYNDROME

Compartment syndrome is one of the most devastating consequences of orthopedic extremity trauma and is the source of significant morbidity and mortality (see also Chapter 98). Compartment syndrome results when interstitial pressure becomes greater than perfusion pressure leading to microvascular collapse, muscle necrosis, and cellular death. It is essential to be able to recognize impending compartment syndrome, as a delay in fasciotomy can be disastrous. The signs of compartment syndrome include pain out of proportion to exam, pallor in the limb, paresthesias, pulselessness, and poikilothermia. In patients who are awake and alert, the diagnosis can often be made based on clinical symptoms confirmed by direct measurement of the compartment pressures. The diagnosis is often more elusive in the obtunded patient and there is often a lower threshold to empirically perform a two-incision fasciotomy. Compartment pressure measurements of greater than 30 mm Hg or a pressure gradient between the diastolic blood pressure and the compartment pressure of less than 30 mm Hg indicates increased compartment pressures and should warrant consideration of decompression.

TENTING SKIN

Bone fragments in closed fractures may spontaneously fall out of reduction and pierce the skin or show evidence of pressure against the dermal layers. These pressure-sensitive areas can eventually necrose and cause a loss of skin coverage. This process then converts a closed fracture into an open fracture and is associated with significant morbidity.

FAT EMBOLISM SYNDROME

Fat embolism syndrome results from fat macroglobules, originating in the long bone marrow, embolizing and causing damage to endothelium. It can resemble respiratory failure and ARDS and is most commonly seen in patients with long bone fractures, concomitant head and pulmonary injury, after reaming of the intramedullary canal, and in patients with multiple trauma involving the thorax and abdomen. In addition to pulmonary symptoms, fat embolism syndrome often manifests with neurologic (agitation or delirium), hematologic (anemia or thrombocytopenia), and dermatologic (petechial rash) abnormalities. Diagnosis is made by using a constellation of symptoms, signs, and laboratory values. Findings are mostly nonspecific, and treatment is controversial but usually supportive.

DEEP VEIN THROMBOSIS (DVT) AND PULMONARY EMBOLUS (PE)

Patients with fractures, unreduced dislocations, and soft-tissue trauma are at a significantly increased risk for the development of DVT or PE. Anticoagulation in the orthopedic trauma patient is critical, but the risk of bleeding must be considered in patients with concomitant spine or head injuries. Frequently, subcutaneous heparin is used, as it can be stopped or reversed prior to operative intervention.

NEGATIVE PRESSURE WOUND THERAPY (NPWT)

Negative pressure wound therapy represents a type of dressing utilized to aid in the formation of granulation tissue and help limit infection. The dressing consists of a sponge that fits within the wound and is then sealed over with an adhesive sheet. The dressing is connected through tubing to a wound vacuum, which must remain on at all times. This type of dressing is prone to loss of seal, and the vacuum device will often alert if there is a leak. It should be noted that NPWT dressings have the potential to become a significant source of occult blood loss. Injured vessels may continue to bleed as a result of the negative-pressure system causing substantial blood loss.

Specific Orthopedic Injuries and Related Procedures

GUNSHOT INJURIES

The management of fractures and soft-tissue injuries as a result of gunshot wounds are controversial. There remains debate as to whether such injuries are truly open fractures. Gunshot wounds resulting from high-energy projectiles (> 2000 m/s) are usually treated as open fractures with immediate antibiotic administration, tetanus prophylaxis (Table 96.E1), emergent debridement and irrigation, and stabilization of bone and soft tissue. The management of low-energy projectiles (handguns) is more controversial. Some physicians consider these injuries "closed." However, if there is concern for contamination, signs of infection, or neurovascular compromise, early operative intervention should be considered. In addition, patients with gunshot injuries (regardless of the presence of a fracture) should always be considered at risk for a compartment syndrome.

PELVIC RING INJURIES

The pelvis is the supporting structure for the peritoneal contents and retroperitoneal structures. It connects the appendicular skeleton to the axial skeleton. Because the pelvis lies in close proximity to vessels, bowel, and genitourinary structures, pelvic ring injuries are often associated with injury to one or more of these structures.

Pelvic fractures are classified as stable, rotationally unstable, or rotationally and vertically unstable. All unstable injuries involve disruption of the posterior portion of the pelvic ring. Unstable pelvic fractures result from high-energy injuries usually in the setting of multiple trauma and are associated with 50% mortality. Such injuries represent an emergency and require rapid assessment, stabilization, and triage.

Patients with pelvic fractures should have a full trauma survey including a thorough neurologic examination. The anterior and posterior pelvis should be inspected for open wounds. In males, the scrotal contents should be palpated and assessed for testicular displacement and the penile meatus should be examined for blood, which would suggest urethral injury. Rectal examination should be performed to evaluate for possible laceration and prostate displacement. Female patients should undergo both bimanual and speculum examinations to rule out vaginal, urethral, and bladder injury.

FRACTURE BLISTERS

Fractures result from mechanisms in which significant energy is transferred to bone through soft tissue. The injured bone and microvascular/lymphatic damage result in significant inflammation in the surrounding soft tissue. This can result in the development of large serous or blood-filled blisters near the fracture site, called *fracture blisters*. Disruption of these blisters is not recommended as the blister serves as a biologic dressing.

TABLE 96.E1 ■ **Indications for Tetanus Prophylaxis**

Tetanus Immunization (Prior Doses of Tetanus Toxoid)	*Clean, Minor Wounds*		*Contaminated Wounds*	
	Tetanus Toxoid	Tetanus Immune Globulin	Tetanus Toxoid	Tetanus Immune Globulin
Uncertain or < 2	Yes	No	Yes	Yes
2	Yes	No	Yes	No*
≥ 3	No†	No	No‡	No

*Yes, if wound greater than 24 h old.
†Yes, if more than 10 years since last dose.
‡Yes, if more than 5 years since last dose.
Adapted from Behrens F: A primer of fixator devices and configurations. Clin Orthop 241:5-14, 1989.

Pelvic ring injuries require prompt diagnosis and treatment. Reducing the volume of the pelvis can be an effective measure to tamponade pelvic bleeding from a venous source (i.e., large pelvic veins). Posterior pelvic disruption can result in 3 to 4 L of blood loss and hemodynamic instability. Aggressive resuscitation is often necessary and may require blood product administration to achieve adequate hemodynamic stability. Patients who do not respond to resuscitative efforts should be continually reevaluated to avoid a missed diagnosis causing ongoing hypotension. If other injuries have been ruled out, then the patient should undergo angiography of the pelvic vasculature after adequate reduction in pelvic volume. If a "blush" or active arterial bleed is visualized on angiography, it can be embolized at the time of the study. The most common source of arterial bleeding in the pelvis is injury to the superior gluteal artery.

To stabilize a pelvic fracture initially, a circumferential binder (bed sheet, commercially available wrap [e.g., T-pod]) can be placed around the pelvis and greater trochanters in order to reduce the intrapelvic volume. After 24 hours, it is imperative that the underlying tissue be assessed for soft-tissue pressure necrosis. Another option for the management of bleeding associated with pelvic fractures is percutaneous external fixation. External fixation is a temporary measure before definitive open reduction and internal fixation. If pelvic stabilization is not possible or bleeding continues despite the application of an external fixation device, angiography and embolization are therapeutic alternatives.

Radiographic assessment of the pelvis includes an AP view along with inlet and outlet views. Further evaluation can be obtained with pelvic CT and a cystogram or retrograde urethrogram. Most patients with unstable pelvic fractures are admitted to the ICU after temporary stabilization of their pelvis. The use of a circumferential binder, although often adequate to reduce the fracture and control bleeding, does not provide extraordinary mechanical stability. Vigilance in the assessment of associated injuries should be maintained until the patient has stabilized.

Once patients are stabilized hemodynamically, they should return to the OR for definitive care of unstable pelvic fractures. Stabilization of these fractures leads to earlier patient mobilization, minimizes the risk of pulmonary complications, decreases time on the ventilator, and improves morbidity and mortality.

ACETABULAR FRACTURES

Acetabular (hip socket) fractures are complex and are frequently associated with significant injury to the hip and can result in lifelong disability. Most acetabular fractures require temporary skeletal traction to maintain the reduction and prevent soft-tissue contracture, with eventual ORIF of the articular injury.

Radiographic evaluation of acetabular fractures includes AP, obturator oblique, and iliac oblique views (collectively called Judet views) of the pelvis. After reduction of the dislocation, a CT scan of the acetabulum should be performed with 1- to 2-mm cuts. Acute management of acetabular fracture/dislocations includes temporizing skeletal traction. Delayed ORIF is the treatment of choice for displaced fractures, instability, or incongruent reductions of the joint. Definitive operative intervention is usually from 2 to 7 days postinjury, which reduces the chance for bleeding complications at the operative site.

TRAUMATIC AMPUTATIONS

Traumatic amputations can result in significant morbidity and potentially dysfunctional limbs (Fig. 96.E5). Therefore, amputation injuries should be handled at institutions under the direction of a team whose care is directed by a microvascular surgeon. Amputations are true limb- and life-threatening injuries and should be handled as such, with no delays in treatment. Unsuccessful



Figure 96.E5 Severely crushed left upper extremity traumatically amputated after a motor vehicle collision with prolonged extraction presenting with gross contamination, loss of neurologic structures, limited soft-tissue coverage, and no remaining bony anatomy. Salvage was not possible.

reimplantations can result in significant disability. Realistic expectations should be provided to the patient only after evaluation by the multidisciplinary team. Amputated parts should be wrapped in sterile gauze moistened with sterile saline solution and then placed in a watertight plastic container or resealable plastic bag, which should then be placed into an iced saline bath. Tetanus prophylaxis (see Table 96.E1) and broad-spectrum antibiotics should be administered, similar to all open fractures (see Table 96.2). Factors associated with a poor outcome include crush injury, long ischemia time (> 6 h), proximal amputations, nerve injuries (axonotmesis), systemic hypotension, severe contamination, concomitant injuries or medical conditions, advanced age, and malnutrition.

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CHAPTER 97

Abdominal Trauma

Scott A. Keeney ■ Jose L. Pascual

The importance of trauma as a public health epidemic cannot be overstated. It is the leading cause of death in Americans under the age of 45. Additionally, traumatic injuries are responsible for the greatest total number of years of life lost and the highest lifetime cost per death when compared with other diseases. In most regions of the United States, blunt mechanisms of abdominal injury such as motor vehicle collisions, falls, and assaults predominate over penetrating mechanisms such as gunshot wounds, stabbings, and other impalements. In urban centers, however, penetrating trauma may represent up to half of all trauma admissions.

The initial assessment of trauma patients is described in Chapter 96, and this chapter focuses on traumatic abdominal injuries.

Initial Assessment

Patients presenting with known or suspected abdominal trauma require a detailed physical examination of the abdomen, which should include inspection, making careful note of cutaneous ecchymosis from seat belts, tire marks, and bullet or stab wounds. Abdominal distention may suggest intra-abdominal hemorrhage, whereas a scaphoid abdomen suggests a ruptured diaphragm. Palpation should focus specifically on the presence or absence of masses or areas of tenderness. Auscultation of the abdomen should be performed as well in order to rule out any pathologic vascular murmurs.

Initial laboratory work should include a complete blood count, serum electrolytes, renal function, coagulation studies, blood typing, urinalysis, and a pregnancy test in women. Other beneficial studies may include tests of liver function, amylase and lipase, serum ethanol level, and a toxicology screen.

Routine radiologic studies obtained in patients with major blunt trauma should include a supine chest radiograph and a pelvic radiograph. Abdominal radiographs are rarely helpful in the assessment of blunt abdominal trauma but are essential in cases of penetrating abdominal trauma. All foreign bodies must be accounted for by abdominal radiologic imaging and also in adjacent images of the thorax, pelvis, and extremities. Entrance and exit sites should be identified with radiopaque markers applied to the patient prior to exposure of the film in order to help determine missile trajectory and potentially injured organs. Trajectory delineation in the initial assessment may quickly determine the need for operative intervention.

Most instances of hypotension in the immediate peri-trauma period should be treated aggressively with volume, using saline or blood products as needed. Although a secondary survey is always necessary, in the setting of life-threatening injuries requiring immediate transfer to the operating room, the exam may have to be delayed until the patient arrives to the intensive care unit (ICU). On arrival to the ICU and after the patient is hemodynamically stable, it is imperative to review all identified injuries and complete the physical exam and

Additional online-only material indicated by icon.

Many patients have absolute indications for surgery that are apparent early in the evaluation (Box 97.E1).

BOX 97.E1 ■ Indications for Immediate Operative Intervention

Blunt Abdominal Trauma

- Hemodynamic instability despite volume resuscitation
- Diffuse peritonitis
- Positive diagnostic peritoneal lavage (DPL)
- Evidence of diaphragmatic rupture

Penetrating Abdominal Trauma

- All gunshot wounds (nontangential)
- Stab wounds with
  - Evisceration
  - Blood per rectum or in the nasogastric tube
  - Positive diagnostic peritoneal lavage (DPL)
  - Hemodynamic instability despite volume resuscitation
  - Diffuse peritonitis
  - Mental status changes precluding reliable serial abdominal examinations

diagnostic workup. The tertiary survey should also be performed in the ICU, generally within 24 to 48 hours after admission to identify any missed injuries. In severely injured patients, the secondary survey is often hindered by life-threatening priorities, and a missed injury rate of 0.3% to 12% has been reported. Although these missed injuries are rarely life threatening, they may be clinically debilitating and can significantly impact the patient's long-term outcome.

All patients with either blunt or penetrating abdominal trauma should be given tetanus prophylaxis if they have not received it in the previous 10 years. If an exploratory laparotomy is planned, a preoperative dose of broad-spectrum antibiotics covering gram-negative aerobes, gram-positive cocci, and anaerobic organisms should be given 30 to 60 minutes prior to incision. If no enteric contamination has occurred, no further antibiotics are required postoperatively. With enteric spillage, however, a 24-hour postoperative course of antibiotics is warranted. As a precautionary measure, all intravascular lines placed in the trauma admitting area should be removed within 24 hours of arrival in the ICU and new vascular access should be established in a sterile manner.

Diagnostic Evaluation of the Patient with Blunt Abdominal Trauma

In the hemodynamically stable patient with blunt abdominal trauma, additional diagnostic studies are often necessary to assess the need for less urgent operative intervention. The choice of study may depend on the availability of equipment, the information sought, and the preference of the clinician (Table 97.1). Diagnostic evaluation, however, should never delay operative intervention in patients with a clear indication for urgent abdominal exploration.

COMPUTED TOMOGRAPHY

The advent of computed tomography (CT) has revolutionized the care of patients with abdominal trauma. In addition to identifying the presence of intra-abdominal fluid or air, established criteria allow one to grade the severity of solid organ injury based on the CT findings, thereby helping to determine the necessity of laparotomy. CT also readily visualizes the retroperitoneum, including genitourinary and major vascular structures, as well as osseous structures such as the bony pelvis and thoracic, lumbar, and sacral spines. Newer CT scans possess enhanced image resolution and reduced image acquisition time, rendering this modality almost indispensable in stable patients with abdominal injuries. With newer technology, the ability of CT angiograms to image the vasculature rivals conventional aortography and venography in many cases.

TABLE 97.1 ■ **Comparison of Utility of Diagnostic Modalities**

Site to Be Assessed	FAST	Abdominal CT	Peritoneal Lavage
Free fluid	+ +	+ ++	+ ++
Hollow viscus	0	+	+
Retroperitoneum	+	+ + +	0
Solid viscus	+ +	+ + +	+ +

0, no utility; +, fair utility; + +, good utility; + + +, excellent utility.
FAST, Focused Assessment of Sonography for Trauma; CT, computed tomography.

Ultrasonography: The Focused Assessment of Sonography for Trauma (FAST)

Ultrasonography has increased in popularity for the rapid assessment of trauma patients and is now part of the initial resuscitation as directed by Advanced Trauma Life Support (ATLS) protocols. This is in part due to easy bedside acquisition and the immediate availability of the information it yields, in addition to the lack of radiation exposure. The Focused Assessment of Sonography for Trauma (FAST) is a quick, reproducible, easily learned technique that evaluates the torso for the presence of abnormal fluid collections. The exam involves interrogation of the chest, looking for pericardial fluid as well as hemo/pneumothoraces, and examination of the abdomen, looking for fluid in dependent areas (the hepatorenal recess, the splenorenal recess, and the pelvis). When used as a rapid triage tool by experienced operators, the technique has been validated in multiple studies with sensitivities in the 70% and high 80% range and specificities reported up to 100% in patients with blunt abdominal trauma and hypotension.

DIAGNOSTIC PERITONEAL LAVAGE (DPL)

Historically, many favored DPL as the primary diagnostic tool for evaluating the abdomen following severe trauma. Controversy still exists, however, regarding the threshold values (red and white blood cell counts and presence of particulate matter) in the effluent that constitutes a positive study. In blunt injury, a red blood cell (RBC) count greater than 100,000/μL is generally considered an indication for laparotomy. However, because blood in the lavage fluid is a nonspecific indication of injury, relying solely on DPL RBC counts may result in a high rate of negative laparotomies (up to 28%). White blood cell (WBC) counts are also unreliable indicators of injury, particularly if obtained early after injury (i.e., before white blood cells have migrated into the peritoneal cavity). DPL is a poor diagnostic tool to evaluate retroperitoneal structures and may carry significant risk in patients with prior abdominal surgery.

RADIOGRAPHIC STUDIES

Plain Radiographs

The value of a chest radiograph in the evaluation of a patient with penetrating abdominal trauma cannot be emphasized enough. Intrathoracic or mediastinal trajectory is often impossible to predict on physical exam alone. A portable chest radiograph, obtained after the primary survey, will quickly identify potentially life-threatening injuries such as a pneumothorax or hemothorax. In the hemodynamically stable patient, plain radiographs of the abdomen or pelvis can often help in further identifying missile trajectory and foreign body retention, allowing the construction of trajectories and the ability to accurately predict which organs are at risk.

Computed Tomography (CT)

CT is uncommonly used in the setting of penetrating abdominal trauma, primarily because it delays operative intervention. The major drawback to CT is the inability to diagnose small bowel injuries, the second most frequent organ injured in abdominal gunshot wounds. However, there are circumstances where the test can be of some value. In the hemodynamically stable patient with a gunshot wound in the right upper quadrant, for example, CT may provide an adequate assessment of the bullet's trajectory, establishing a trajectory confined to the liver. Such a finding would allow management to proceed nonoperatively. CT with rectal contrast may be useful in the evaluation of a patient with a transpelvic gunshot wound, ruling out rectal and bladder (CT

Because of the rapidity and sensitivity of ultrasonography and CT in diagnosing hemorrhage, many have referred to the technical skill required to perform DPL as a lost art. A retrospective review of patients undergoing DPL in a level I trauma center over a 10-year period showed a steady decline in the annual utilization of this modality, despite an accuracy rate of 100% in predicting the need for therapeutic laparotomy in the unstable patient. Most would now agree that CT, ultrasound, and DPL have complementary roles and each must be considered in a particular patient and situation.

Diagnostic Evaluation of the Patient with Penetrating Abdominal Trauma

When evaluating a patient with stab wounds to the abdomen, it is important to consider the location of the wound, the length of the weapon, the trajectory of the injury, and an estimation of the depth of the wound. The issue that has the greatest implication on the urgency for operation is determining if the peritoneum has been violated. Once this has been established, immediate operative intervention is warranted.

In contrast, in patients with abdominal gunshot wounds, peritoneal violation is assumed and laparotomy should be performed immediately in the majority of patients. Delineation of trajectory prior to laparotomy is a fundamental part of injury characterization. Critical elements such as the type of weapon (e.g., handgun or rifle), distance from the assailant, or special ammunition are important factors in arriving at an optimal management plan.

cystography) injury. Useful information about retroperitoneal injury can also be obtained from CT images.

LOCAL WOUND EXPLORATION

Local wound exploration is a technique where an anterior abdominal wall stab wound is explored in a formal manner in the emergency department prior to formal operative intervention in the operating room (OR). The wound is prepped in a sterile manner, and a local anesthetic is injected in the surrounding area. An exploration is considered positive if the anterior fascia is violated. It may be necessary to extend the skin wound in order to determine if this is the case.

LAPAROSCOPY

In a hemodynamically stable patient with equivocal peritoneal penetration, there may be utility in performing a diagnostic laparoscopy. This method allows visualization of the peritoneal surface but is less effective at assessing for other associated injuries such as bowel perforation or retroperitoneal injury. Additionally, in patients with lower thoracic wounds, if peritoneal penetration is established, the laparoscope may be particularly useful to interrogate the diaphragm. If there is a diaphragmatic injury, operative intervention is warranted.

Management

BLUNT ABDOMINAL TRAUMA

CT has drastically altered how blunt abdominal trauma patients are managed. With the availability of rapid, high-resolution images of the abdomen, the surgeon can now reliably determine the extent of injuries and formulate an appropriate management strategy.

Hemodynamically stable patients with solid viscous injury are typically admitted to the ICU for observation. They are kept on strict bed rest and given nothing by mouth. Serial abdominal examinations, as well as serial hemoglobin checks, are necessary. Abnormalities in clotting factors should be corrected with blood products and vitamin K. Although there is no consensus on an absolute transfusion requirement that should trigger operative intervention, hemodynamic instability or a change in location or severity of the abdominal pain should always prompt reassessment and consideration for laparotomy.

Operative management of solid organ injury from blunt trauma depends on the stability of the patient. Hemodynamic instability with splenic trauma always mandates splenectomy. However, in the hemodynamically stable patient with isolated splenic injury, a salvage procedure may be attempted, which includes partial splenectomy or splenorrhaphy. The hemodynamically unstable patient with hepatic injury poses a more complex challenge.

Angiography and angioembolization have become indispensable in the current management of abdominal trauma. They represent the imaging and therapeutic modalities of choice for pelvic fractures associated with extraperitoneal hemorrhage and are often attempted even when the patient is hemodynamically unstable. In the hemodynamically stable patient with solid organ injury, the role of angiography is less clearly defined. High-risk lesions, such as active solid organ bleeding (seen as contrast extravasation on CT), vascular injury, and high-grade injury, have all been managed successfully with interventional radiographic techniques. The goals of embolotherapy are to stop the bleeding and stabilize the patient. In less than 10% of cases, angioembolization may be unsuccessful. In these cases, operative intervention is necessary. It is imperative that a multidisciplinary approach be used to make these critical decisions, bringing together the intensivist, anesthesiologist, interventional radiologist, and trauma surgeon.

DIAGNOSTIC PERITONEAL LAVAGE

Some authors have advocated DPL as a method to determine if intra-abdominal injury has occurred in the patient with an abdominal stab wound. In this setting, the RBC and WBC levels that constitute a positive study are much lower than in patients with blunt trauma. However, precise levels that indicate the need for operative intervention remain unclear and consensus is lacking. Furthermore, DPL is limited in penetrating abdominal trauma because of the inability to discriminate rupture of the diaphragm or injury to retroperitoneal structures.

Cothren et al validated this approach in patients with an anterior abdominal wall stab wound without an immediate indication for laparotomy and reported that only 11% of patients required surgical intervention. Most of their patients without anterior fascia violation were discharged directly from the trauma admitting unit.

PENETRATING ABDOMINAL TRAUMA

All patients with a penetrating abdominal injury and hemodynamic instability, or signs of peritoneal injury, require urgent exploratory laparotomy. However, in the cooperative, hemodynamically stable patient without peritoneal signs, many surgeons will elect nonoperative management and observation of the penetrating wound. This practice requires serial abdominal examinations and a low threshold to perform an exploratory laparotomy if clinical deterioration occurs.

DAMAGE CONTROL

"Damage control" is a technique used in the management of critically ill patients with blunt or penetrating trauma. Patients with severe multisystem trauma are particularly susceptible to the development of a coagulopathy secondary to hypothermia, acidosis, and hemodilution, coupled with ongoing hemorrhage. If left untreated, such a constellation of problems will inevitably lead to death. Damage control techniques are designed to break the self-perpetuating deterioration and have been validated to salvage many of the most critically injured patients who would not otherwise survive. Box 97.1 shows common indications for damage control laparotomy.

Damage control occurs in four phases.

In phase I, patients undergo an expeditious exploratory laparotomy to stop obvious hemorrhage and limit contamination from hollow viscus perforation. Laparotomy packs may be left in the abdomen for tamponade and hemostasis.

In the second phase, the patient is brought to the ICU where physiology is aggressively treated by volume resuscitation, reversal of acidosis, support of hemodynamics, correction of clotting abnormalities, and rewarming. The development of acidosis, coagulopathy, and hypothermia has been described as "the lethal triad" as it is associated with a high risk of mortality. Large-bore, central venous catheters for volume repletion are used and all fluid and blood products should be warmed to restore normal core temperature as rapidly as possible. Additional measures to rewarm the patient include an environment with a warm ambient temperature, administering warm sterile saline, bladder or stomach irrigation, delivering warm fluid lavage via tube thoracostomy, and the warming of inspiratory gas mixture above 37.0° C. Rapid correction of the coagulopathy with specific blood products, as determined by measured hematologic deficiencies, is essential. These patients occasionally are managed with the aid of a pulmonary artery catheter to determine the appropriate balance of volume and vasoactive medications. Only after achieving normothermia, a normal coagulation profile, and resolution of metabolic acidemia should the patient return to the operating room. Exceptions to this rule include obvious ongoing surgical bleeding or the development of abdominal compartment syndrome. Resuscitation and rewarming in the ICU usually require 24 to 48 hours.

BOX 97.1 ■ Indications for Damage Control

1. Inability to achieve hemostasis owing to a recalcitrant coagulopathy
2. Inaccessible major venous injury (e.g., retrohepatic vena cava, pelvic veins)
3. Time-consuming procedure in the patient with suboptimal response to resuscitation
4. Management of extra-abdominal life-threatening injury
5. Reassessment of intra-abdominal contents (e.g., compromised intestinal blood supply resulting from extensive mesenteric injury)
6. Inability to reapproximate abdominal fascia because of splanchnic reperfusion-induced visceral edema

From Moore EE, Burch JM, et al. World J Surg 22, 1998.

The third phase of damage control involves reexploration; removal of packing; repair, resection, or reconstruction of injured organs; placement of tubes for feeding enteral access (if indicated); and definitive wound closure. More than one packing change may be necessary to achieve hemostasis and allow dissipation of bowel edema.

The fourth phase of damage control is abdominal wall reconstruction and is usually reserved for 6 to 12 months postinjury. During this period of convalescence, intra-abdominal inflammation will abate and a skin graft, if required for closure, should be easily lifted from the underlying abdominal viscera. Reconstruction can be complex and may require consultation with a plastic surgeon.

Postoperative and Posttraumatic Complications

Complications in the postoperative period may prolong ICU length of stay and add to the complexity of management. Prompt recognition and aggressive treatment of such complications if they arise remain the foundation of good ICU care.

MISSED INJURIES

With the increasing use of nonoperative observation for solid organ injury, patients are carefully followed for signs of hollow viscus or pancreatic injuries; both of which are notoriously difficult to visualize on initial imaging. A patient who fails to improve, develops sepsis with an unclear source, or experiences acute respiratory distress syndrome (ARDS) should be evaluated for missed injuries. Patients who undergo abdominal exploration for a life-threatening injury frequently have abnormal anatomy as a result of the destruction of tissues and the distortion of normal anatomic planes by surrounding hematoma or edema. This makes a thorough assessment more difficult and increases the potential for missed injury. Often the more complex the injury and the more unstable the patient, the more likely the possibility of missing an injury during laparotomy.

HEMORRHAGE

Continued bleeding during the postoperative period may occur and may manifest through saturated wound dressings or copious bloody output from abdominal drains. In coagulopathic patients, a distinction must be made rapidly between true "surgical" bleeding that requires immediate operative intervention or coagulopathic bleeding that will abate with correction of acidosis, hypothermia, and clotting factor deficiencies. In general, the postoperative patient should be warmed and resuscitated, and deficiencies of coagulation factors corrected, *prior* to the decision to reexplore the abdomen. Premature return to the operating room in a coagulopathic patient may impart significant additional risk to an already critically ill patient.

INFECTION

Intra-abdominal sepsis in the postoperative ICU trauma patient is not uncommon. This may be the result of perforation of unprepared bowel with gross contamination of the peritoneal cavity. Despite perioperative antibiotics and lavage of the abdomen at the time of postinjury laparotomy, abscesses may develop. Such collections typically develop 5 to 7 days postoperatively and may present insidiously as low-grade recurrent fevers or more dramatically as profound sepsis and multiorgan system failure. Definitive diagnosis is often made with the assistance of CT. Drainage of intra-abdominal collections is required by an open, operative approach or by a radiologically guided percutaneous catheter approach.

ABDOMINAL HYPERTENSION

Risk factors for the development of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) include severe abdominal trauma resulting in visceral edema, intra-abdominal or retroperitoneal hemorrhage, or the presence of intra-abdominal packs. When present, ACS may manifest as oliguria (from decreased renal perfusion), elevated peak airway pressures (transmitted from the intra-abdominal compartment), and low cardiac output (from a reduction in venous return due to inferior vena caval [IVC] compression). Bladder pressures are obtained as a surrogate for intra-abdominal pressure and can be measured at the bedside using sterile water injected into an indwelling Foley catheter. Normal pressures range from 0 to 4 mm Hg, but pressures as low as 10 to 15 mm Hg may have significant clinical repercussions. Pressures greater than 20 mm Hg should prompt consideration for decompressive laparotomy. In this setting, severe bowel edema may require delayed abdominal closure after proper diuresis and resolution of edema. It must be remembered that ACS may occur, or reoccur, in patients with an open abdomen and that temporary abdominal closure does not eliminate all risks for ACS.

Summary

Patients with abdominal trauma require rapid assessment and resuscitation. Life-threatening injuries should be identified early and treated aggressively. As the indications for operative intervention for patients with abdominal trauma have declined, a multidisciplinary approach to the care of these patients is warranted.

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CHAPTER 98

Extremity and Major Vascular Trauma

Adam M. Shiroff ■ Patrick K. Kim

Extremity Trauma

Major injury to the extremities can result in damage to vessels, nerves, or soft tissue within the fascial compartments. When a patient with such injury arrives in the intensive care unit (ICU), these areas demand immediate and ongoing assessment by the ICU team.

PERIPHERAL VASCULAR INJURIES

Penetrating trauma to the extremities produces a spectrum of injury to the vessels that lie within the trajectory, ranging from partial disruption to complete transection. In addition, *gunshot wounds* involve the transfer of kinetic injury from the projectile to surrounding tissues ("blast effect") resulting in injury to vessels not directly within the path of the bullet. The mechanisms of vascular injury with *blunt trauma* are myriad but frequently include compression, traction, and deceleration forces that can cause intimal disruption, thrombosis, and avulsion of vessels. Fractures and dislocations caused by blunt injury can secondarily cause vascular damage.

Diagnosis

Regardless of the mechanism of injury, the affected extremity should be examined for active hemorrhage, hematoma, or a palpable thrill. Perfusion is evaluated by inspection of skin color, palpation of distal pulses, assessment of venous refilling and capillary refill, and determination of neurologic function. Areas of paresthesia, hypesthesia, or paralysis usually correlate with arterial injuries. Table 98.1 lists "hard" (more definitive) and "soft" (more equivocal) signs of vascular injury.

The ankle-brachial index (ABI) is calculated by dividing the systolic pressure in the traumatized extremity by the systolic pressure at the brachial artery. An ABI of less than 0.9 indicates major vascular injury but should be considered a "soft" sign because it does not mandate surgical exploration by itself.

Patients who present with "hard" signs require no additional diagnostic testing prior to intervention. In patients with "soft" signs, particularly in those with an ABI of less than 0.9, the next diagnostic modality of choice is arteriography. With the exception of knee dislocation, in the absence of "hard" findings, proximity of the injury to a major vessel is not an absolute indication for arteriography. Arteriography is always recommended after knee dislocation to rule out blunt injury to the popliteal artery, as well as after shotgun wounds because of the multiple small projectiles. The use of computed tomography angiography (CTA) is becoming more frequent and is considered an excellent diagnostic tool for the assessment of vascular injury in an otherwise stable patient. The availability of CTA allows for rapid diagnosis and, if vascular injury is seen, can prompt either endovascular or surgical intervention. Although many non-invasive diagnostic modalities are not widely available and can be difficult to perform or interpret, the use of duplex ultrasonography is appropriate in patients with "soft" signs and an ABI greater than 0.9.

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Operative Interventions

Patients with "hard" signs should be immediately transported to the operating room (OR) or interventional radiology (IR) suite for surgical exploration or repair. An intraoperative arteriogram may be performed if ongoing diagnostic information is necessary. Major arterial injuries are initially controlled with vascular clamps, resection of the injured segment of artery, and placement of an interposition graft to restore flow. Restoration of flow with smaller arterial injuries can sometimes be achieved with a primary anastomosis or use of a vein patch. An intraluminal shunt may be used to perfuse the extremity temporarily while other injuries are addressed (e.g., unstable fracture). Arterial reconstructions should always be evaluated at the end of the operation with an intraoperative arteriogram.

Large venous injuries are usually repairable; however, with the exception of the popliteal vein, they can usually be ligated if necessary. The decision to ligate is based on the hemodynamic stability of the patient and the complexity of the injury.

The surrounding fascia should be opened to release surrounding pressure on the vasculature (i.e., fasciotomy) when there has been a significant delay in restoration of perfusion, preoperative hypotension, significant swelling or crush injury to the extremity, combined arterial and venous repairs, or ligation of a major vein.

TABLE 98.1 ■ **Signs of Peripheral Vascular Injury**

"Hard" Signs	"Soft" Signs
Distal pulse deficit	Adjacent nerve injury
Expanding or pulsatile hematoma	Diminished pulse (or ankle-brachial index < 0.9)
Palpable thrill or audible bruit	Moderate visible hemorrhage
Visible arterial hemorrhage	

Postoperative Care

The goals of postoperative care are resuscitation of intravascular volume, rewarming, and correction of acidosis. Acidosis, hyperkalemia, and edema often result from reperfusion of the ischemic extremity. The degree in which they occur is directly proportional to the time and total area of tissue that sustained malperfusion. Frequent assessment of the integrity of the affected vascular bed is essential in the postoperative period. If any compromise in circulation is suspected, the surgeon must be notified immediately. Because pulses are not always palpable postoperatively, as a result of vasoconstriction and hypothermia, capillary refill can be used to assess the adequacy of perfusion. Elevation and elastic wrapping of the extremity can help to minimize edema formation, particularly after venous ligation or repair. In these cases, and particularly if a fasciotomy was not performed, the extremity must be evaluated frequently for signs and symptoms of compartment syndrome (discussed later).

Thrombosis of an arterial reconstruction should be suspected when a discrepancy exists between pulses or when the ABI falls to less than 0.9 in the normothermic patient. Although edema is a universal complication, especially after venous ligation, edema may also indicate thrombosis at the site of a venous repair. When present, the surgeon must be identified immediately as these patients may require an immediate return to the operating room to restore perfusion.

Bleeding in the postoperative period may be due to coagulopathy, incomplete ligation of small vessels, or dehiscence of an arterial suture line. Coagulopathy should be reversed with appropriate blood component therapy as guided by coagulation parameters (see Chapter 19). Careful inspection of the wound and estimation of the degree of hemorrhage can often help to differentiate simple wound bleeding from suture line dehiscence.

PERIPHERAL NERVE INJURIES

Categories of Nerve Injuries

Injuries to peripheral nerves often accompany vascular trauma and are classified by histologic changes and associated neurologic insults.

Neurapraxia occurs most frequently after blunt trauma and is characterized by local physiologic loss of axonal conduction. Patients typically present with isolated motor paralysis and sparing of sensory and autonomic function. Because the distal axon remains intact and there is preservation of electrical conductivity, full recovery can usually be achieved with conservative management.

Axonotmesis refers to axonal injury with preservation of the endoneurium (connective tissue elements) and occurs most commonly after blunt trauma or traction. Wallerian degeneration produces motor, sensory, and autonomic dysfunction with subsequent distal muscle atrophy. Nerve regeneration occurs at a rate of 1 mm/day. Functional recovery is influenced by age, associated injuries, and the peripheral level of injury (proximal versus distal). Surgery may be indicated for patients who fail to recover function.

Complete or partial transection of the nerve is defined as *neurotmesis* and is characterized by a complete loss of motor, sensory, and autonomic function and leads to distal muscle

Graft infection rarely complicates the early postoperative period. Wound infection, however, must be considered in the febrile patient because groin incisions are frequently used for lower-extremity vascular trauma. Proximity of injury to the perineum and interruption of the lymphatics both predispose to infection.

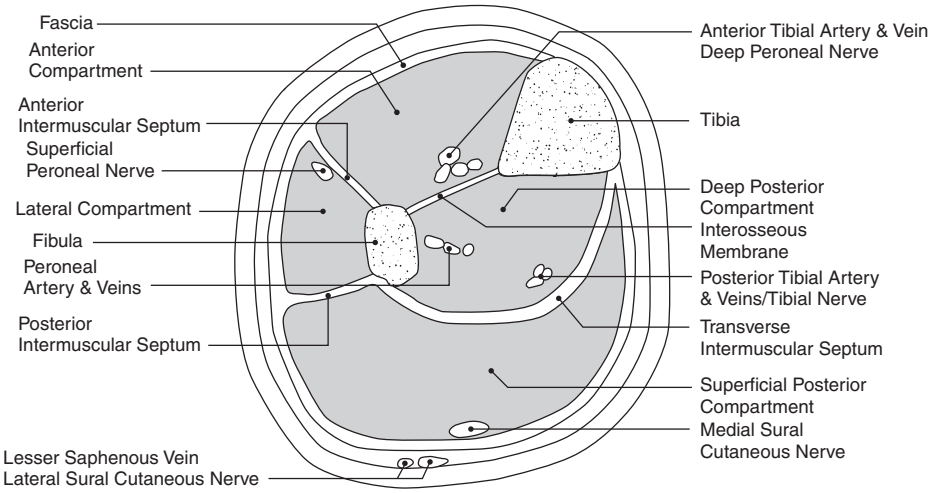


Figure 98.1 Cross-section of the lower leg showing the four major fascial compartments and their associated nerves and vessels.

atrophy. Lack of connective tissue support can result in misrouting of regenerating nerves and formation of painful neuromas. Surgical intervention is indicated in these patients if they are otherwise expected to have a meaningful overall functional recovery from their other traumatic injuries.

Diagnosis

The diagnosis of peripheral nerve injury can usually be made with a careful history and physical examination. Determination of sensory deficits helps to delineate the level of the injury (see Figure 101.1 in Chapter 101 for sensory dermatomes). Electromyographic testing defines the injury type and has prognostic value but should be delayed until 3 to 4 weeks after injury. Treatment may involve surgery in cases where the injury is severe. Because injured extremities are at risk for muscle atrophy, joint stiffness, fibrosis, and trophic skin changes, early physical therapy is essential for an optimal outcome (see Chapter 21).

COMPARTMENT SYNDROME

Because the muscles, nerves, and vasculature of the extremities are enveloped in fascial compartments (Figure 98.1), edema may increase the pressure within the compartment and prevent effective venous return (Box 98.1). When pressure within a fascial compartment exceeds capillary perfusion pressure, tissues in that compartment are subject to ischemia and ultimately cell death. Although compartment syndrome occurs most often in the lower leg, other compartments—for example, those in the arm or buttocks—can also be affected.

Diagnosis

In conscious patients, early clinical features of compartment syndrome include weakness, hypesthesia, palpable fullness, and pain out of proportion to that expected by the clinical setting or with passive stretch (dorsiflexion). Assessment of distal pulses alone is an *insufficient* monitoring modality because pulse deficits typically develop well *after* irreversible muscle damage has occurred. The same applies to paralysis and sensory deficits, both of which also are *late findings* and suggest muscle necrosis.

BOX 98.1 ■ Risk Factors for Compartment Syndrome

Arterial injury or combined arteriovenous injury
Burns (circumferential or electrical)
Crush injury (extensive soft tissue trauma)
External compression (casts, splints, and so on)
Fracture (open or closed)
Prolonged ischemia of the extremity (vascular occlusion, hypotension)
Severe venous occlusive disease

BOX 98.2 ■ Neurologic Signs of Blunt Injury to Carotid Artery

Ipsilateral Horner syndrome
Limb paresis in an otherwise neurologically intact patient
Lucid postinjury period before onset of neurologic signs
Transient attacks of cerebral ischemia

If compartment syndrome is suspected in an unconscious patient, compartment pressures should be measured. Pressures are measured in a standardized manner by inserting a fluid-filled catheter connected to a pressure transducer into each of the compartments in question.

Management

Fasciotomy is traditionally indicated for compartment pressures > 40 mm Hg, for pressures between 30 and 40 mm Hg for 4 hours or more, or for pressures less than 30 mm Hg with concomitant clinical findings. However, a diagnosis of compartment syndrome based solely on the absolute intracompartmental pressure is an oversimplification because the ischemia results from compromised *perfusion pressure*. Hence, current recommendations are that a diagnosis of compartment syndrome should be made based on the "delta pressure" (diastolic blood pressure minus intracompartmental pressure). *A delta pressure less than or equal to 30 mm Hg is diagnostic of compartment syndrome and warrants fasciotomy.*

Vascular Injuries of the Neck

DIAGNOSIS

Blunt injury to the carotid artery can be difficult to diagnose. Overt signs of neck trauma may be absent and clinical signs of carotid artery injury may be insidious (Box 98.2). Furthermore, neurologic assessment is limited in these patients because of associated head trauma. Under these circumstances, one must rely on physical examination and a high index of suspicion based on the mechanism of injury. Suspicion of blunt carotid injury should prompt an arteriographic evaluation. Modern screening of blunt cerebrovascular injury (BCVI) is performed with CTA of the neck. Criteria to prompt such screening include the Denver criteria, which include (1) signs/symptoms of BCVI: arterial hemorrhage from the nose or mouth, expanding cervical hematoma, or neurologic defects unexplained by traumatic brain injury, and (2) risk factors for BCVI: high energy transfer, LeFort II or III skull fractures, cervical spine fractures involving C1-C3, carotid canal involvement with basilar skull fracture, diffuse axonal injury with Glasgow Coma Scale (GCS) < 6, anoxic brain injury after hanging, and clothesline-type injury or seatbelt abrasions across the neck. In addition to patients with these high-risk factors, others who may benefit from screening include those with mandible fractures, those with upper thoracic trauma combined with brain injury, and the pediatric population.

In contrast to blunt injury, penetrating neck trauma is usually clinically apparent. Focal neurologic deficits must be sought and documented, and injuries to the trachea or esophagus must be excluded. A large or expanding hematoma requires early definitive airway control. Hemodynamically unstable patients require prompt operative evaluation.

Treatment

Historically, the anatomic zones of the neck determine the diagnostic and therapeutic approach. Zone I of the neck includes those tissues that lie above the transverse plane at the level of the angle of the mandible. Zone III lies below the transverse plane at the level of the cricoid cartilage, whereas zone II is everything between zones I and III. Patients with penetrating trauma to zone II classically went to the OR for exploration, regardless of stability. For patients who are hemodynamically stable and without overt signs of vascular or aerodigestive injury, it is now a well-accepted practice to undertake a "No Zone" approach. This approach refers to an evidence-based, technologically advanced method of evaluating penetrating neck trauma. All injuries should be evaluated using an extensive physical exam that has been shown to be generally as effective in detecting vascular injury as angiography, with a sensitivity of 93% and a specificity of 97%. When combined with the use of CTA, which has a sensitivity of 100% and a specificity of 98.6% for arterial injury, vascular injury can definitively be diagnosed or ruled out. Therefore, a zone-independent approach consisting of a combination of a careful physical exam and multidetector CTA can lead to appropriate diagnostics, triage, and directed intervention in patients with penetrating neck injury. Hemodynamically unstable patients or those with hard signs of injury should be treated operatively. All others should be evaluated using CTA, the diagnostic tool that offers the best combination of speed, precision, and reliability and confers safety and universal applicability regardless of zone of injury.

Postoperative Care

In the absence of significant hematoma, patients should be extubated and sedation minimized to permit rapid and accurate neurologic evaluation. The surgical site requires careful surveillance for the development of swelling or hematoma, both of which can rapidly lead to respiratory compromise. To facilitate venous drainage, the head of the bed should be elevated. Pharmacologic therapy is indicated to avoid extremes in blood pressure.

Postoperative stroke may result from arterial occlusion or thrombosis. If changes in neurologic function (see Chapter 92 for more details) occur, prompt return to the operating room should be considered.

Injuries to the Abdominal Aorta and Visceral Branches

Hemodynamic instability after penetrating or blunt abdominal trauma suggests major vascular injury. Although penetrating wounds are usually detected on physical examination, blunt injuries may be more insidious and manifest only as an abdominal wall contusion or a "seat belt sign." Distal pulse deficits may be present in injuries to the pelvic vessels.

Diagnosis and Treatment

Exploratory laparotomy remains the primary diagnostic modality in hemodynamically unstable patients with penetrating injury. In hemodynamically stable patients with gunshot wounds, preoperative radiographic imaging facilitates trajectory determination. Laparoscopy, diagnostic peritoneal lavage, local wound exploration, and simple observation may be elected for stable patients with stab wounds and tangential gunshot wounds. Ultrasonography has largely replaced diagnostic peritoneal lavage and is used to exclude hemoperitoneum in the unstable patient with blunt trauma. In the hemodynamically stable patient with blunt trauma, computed tomography offers a non-invasive diagnostic modality.

Arteriography is indicated when the kidneys are unable to be visualized on computed tomography. Arteriography may be both diagnostic and therapeutic when an area of high density (suggestive of active hemorrhage) is seen in the liver or spleen. Lower-extremity pulse deficits unexplained by extremity injuries also require arteriographic evaluation.

Postoperative Care

After surgery for major vascular injuries, large fluid shifts can be expected. Monitoring cardiac filling pressures by use of a central venous or pulmonary arterial catheter may facilitate fluid management. Maintenance of normothermia, correction of acidosis, and reversal of coagulopathy are the goals of resuscitation. Although still controversial, current evidence suggests that these goals are best achieved by limited administration of warm crystalloids and aggressive blood and blood product transfusion in a (1:1:1) packed cells, fresh frozen plasma, platelets ratio (see Chapter 19).

The lower extremities of the patient with injured common or external iliac vessels must be carefully monitored for edema, compartment syndrome, and perfusion deficits indicative of thrombosis. If ligation of the common iliac or external iliac vein has been performed, the involved extremity should be wrapped with an elastic wrap and elevated to reduce edema.

Intestinal infarction may result after superior mesenteric artery repair secondary to graft thrombosis. Shock, increased fluid requirement, leukocytosis, and metabolic acidosis are sensitive but not specific indicators to suggest the diagnosis. If this diagnosis is suspected, an arteriogram should be performed promptly to evaluate the patency of the repair.

Oliguria may indicate stenosis of a renal artery repair. Although other causes for oliguria (hypovolemia, acute tubular necrosis, radiographic contrast, or aminoglycoside-induced nephropathy) are possibilities in this clinical setting, the presence of hypertension supports the diagnosis of graft stenosis. To avoid nephrotoxic contrast material, one should use digital subtraction angiography or other noncontrast imaging modalities to evaluate vascular patency.

An annotated bibliography can be found at www.expertconsult.com.

Small injuries to the abdominal aorta can often be repaired primarily. More extensive injuries may require a prosthetic graft. An evolving method of treatment for major vascular injury is placement of endovascular stent grafts. There has been success in treating the thoracic, abdominal, and large peripheral vessels with this technique. Survival rates are greater when the location of aortic injury is infrarenal as compared with suprarenal (a 50% versus 35% survival rate).

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CHAPTER 99

Head Trauma

Zarina S. Ali ■ Matthew F. Philips ■ Mark J. Kotapka ■ Eric L. Zager

Head injury occurs every 7 seconds in the United States, resulting in approximately one death every 5 minutes. It is the leading cause of death among persons under the age of 24 years. Approximately 200,000 patients die or are permanently disabled each year from brain trauma. Sixty percent of traumatic brain injuries (TBIs) are caused by road traffic accidents, 20% to 30% are caused by falls, approximately 10% are caused by violence, and another 10% are due to work- or sports-related injuries. Globally, the burden caused by TBI to patients, caregivers, and society is large and increasing.

Classification of Head Trauma

SCALP INJURY

The head is a multilayered structure composed of the scalp, skull, dura, and brain. The degree to which each layer can withstand injury depends on its tissue composition and relative perfusion. The first layer of brain protection is the scalp. Because the scalp is a highly vascular structure, large scalp lacerations can result in enough blood loss to cause hypovolemic shock. Violation of the scalp with concomitant injury to the skull and dura can lead to intracranial infection.

SKULL INJURY

When the force sustained by the skull is greater than the strength of the skull, the skull fractures. Cranial vault fractures can be classified as open or closed, depending on the integrity of the overlying scalp and underlying dura. Among the various types of fractures, the *linear fracture* is the most common. A simple linear fracture with no scalp violation may only require brief observation to rule out intracranial injury. If the fracture violates perinasal air cavities, however, the risk of cerebrospinal fluid (CSF) rhinorrhea or otorrhea increases; meningitis can also develop when the fracture exposes the epidural space to sinus contents. Such fractures may require surgical intervention. Finally, injury to vascular structures, such as the middle meningeal artery or venous sinuses, can complicate skull fractures and result in potentially lethal epidural hematomas or sinus thromboses.

Depressed fractures result from impact with small surface area objects (< 2 square inches) at high velocities. They may be open or closed and frequently involve vascular structures. If the injury violates both dura and cortex, there may be significant evolution of hematoma and there exists the potential for intracranial contamination from bone fragments, foreign bodies, or both. The management of depressed skull fractures is controversial.

The thin anterior base of the skull is particularly susceptible to injury. The presence of "raccoon's eyes" (periorbital ecchymoses) or Battle's sign (retromastoid hematoma) reliably signifies a skull base

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Irrigation, local debridement, and primary closure are the initial steps of treatment for lacerations. In cases of scalp avulsion with moderate to severe scalp loss, rotational flaps, skin grafting, microsurgical reimplantation, or free tissue transfers may be required. The process of tissue expansion has greatly enhanced scalp reconstruction. Implantation of a subcutaneous silicon reservoir, followed by serial injections of sterile saline into the reservoir over several weeks, can sufficiently stretch the scalp skin for flapping purposes. Up to 50% of the scalp can be replaced with this method.

From a series of 284 patients with depressed fractures, only 2.8% of those treated nonoperatively developed infectious complications. From those data, investigators concluded that the majority of these fractures are best treated conservatively. The following fractures and associated injuries typically require surgical management: gross contamination or established infection, presence of CSF or brain tissue in the wound, a concomitant intracranial lesion requiring surgery, severe bleeding from the wound, frontal sinus involvement, cosmetically unacceptable depressions, and severely comminuted fractures.

Whereas larger fractures within the skull base are usually readily apparent on computed tomography (CT) imaging, smaller fractures are frequently absent on plain film imaging and can be easily missed with CT. If the suspicion for basilar skull fracture remains high despite negative radiographic findings, the diagnosis can still be made on clinical grounds.

fracture. CSF otorrhea or rhinorrhea, hemotympanum, or blood in the external auditory meatus without evidence of direct ear trauma is also a hallmark of these fractures. Skull base fractures can involve the carotid canal and result in carotid rupture, dissection, or thrombosis. When this is suspected, cerebral angiography is indicated to evaluate vessel integrity.

BRAIN INJURY

Focal Brain Injuries

The neurologic presentation of focal brain injury relates directly to the specific region of the brain involved. Global neurologic deficits or coma with focal injuries are usually the result of brain stem compression and require urgent diagnosis and treatment.

In a study of 1448 patients with mild head injury (defined as a Glasgow Coma Scale [GCS] score of 13 to 15; Table 99.E1), the most common lesion was a *contusion*. Contusions often involve the surface of the brain beneath vault fractures, at points where brain the surface collides with bony surfaces of the middle and frontal fossa, or in regions of the cortex where high surface strains are produced by the inner table of the skull. This occurs most commonly in the frontal and temporal lobes but may occur at any site including the brain stem and cerebellum. In patients with focal injuries, the presence of contusion alone tends to portend a good prognosis. *Intracerebral hematomas* result from torn blood vessels in deeper brain structures. They are not contiguous with the cortical surface and typically occur in the deep white matter of the frontal and temporal lobes. Injuries in which the pial surface is violated with parenchymal disruption are termed *cerebral lacerations*.

Epidural hematomas result from injuries that cause disruption of dural vessels, sinuses, or diploic channels, allowing blood to dissect into the epidural space. The middle meningeal artery is frequently injured with temporal bone trauma, resulting in an epidural hematoma.

Epidural hematomas can occur in the setting of a relatively minor head injury and may present with only minor neurologic signs or symptoms. Although they occur in less than 3% of head-injured patients, it is important to have a high index of suspicion because rapid expansion, if not treated immediately, can cause brain compression. Prognosis with epidural hematomas is related to age, GCS at presentation, and the timing of evacuation. Concomitant intracranial injury, such as subdural hematoma, adversely affects outcome.

Subdural hematomas are focal lesions that result from contact or acceleration and inertial forces. When vascular structures of the pial surface are disrupted, bleeding occurs within the subdural space. When the head undergoes rapid deceleration, as in a motor vehicle accident, cortical bridging veins can tear and bleed into the subdural space. In general, subdural hematomas have a poor prognosis because, in contrast to epidural hematomas, they are usually accompanied by a significant parenchymal injury. The morbidity and mortality associated with subdural hematomas are related to the GCS on presentation, age, intracranial pressure (ICP), and mechanism of injury. An evolving hematoma may cause herniation and brain stem compression leading to a decreased level of consciousness. Rapid recognition of this process and immediate treatment are essential.

Diffuse Brain Injury

Concussion and diffuse axonal injury represent two ends on the spectrum of diffuse brain injury. Typically with diffuse brain injury there are no grossly evident intracranial lesions. As a result, alterations in level of consciousness result from global or diffuse disruption of the anatomic and physiologic neural substrates rather than brain stem compression. The perturbation lies at the level of the neuronal cell membranes and axolemmas and can be widespread in both the cerebrum and brain stem.

Concussion is a mild form of global neurologic dysfunction. The exact mechanism and pathophysiology of concussion remain an enigma. The neurologic disturbances seen in concussive syndromes may relate to the magnitude and site of head injury. Although concussion may or may

TABLE 99.E1 ■ **Scoring for Glasgow Coma Scale***

Eye Opening		Verbal		Motor	
Best Function	**Score**	**Best Function**	**Score**	**Best Function**	**Score**
Spontaneous	4	Oriented	5	Follows commands	6
To voice	3	Disoriented	4	Localizes	5
To pain	2	Inappropriate	3	Withdraws	4
No response	1	Incomprehensible	2	Flexes	3
		No response	1	Extends	2
				No response	3

*The Glasgow Coma Scale is calculated as the sum of the highest scores from each of the three categories listed. The maximal score is 15 and minimal score is 3.

Fractures through any of the skull base foramina can cause specific cranial nerve injuries. The delicate neurons of the olfactory nerves that pass through the cribriform plate are especially prone to disruption. As with the linear fractures, operative repair is usually not indicated for skull base fractures unless there is persistence of CSF leak or compromise of vascular or neural tissue. Pulsatile exophthalmos, ophthalmoplegia, chemosis, or a bruit with visual loss should alert the examiner to a possible carotid-cavernous sinus fistula, which may require immediate endovascular or, rarely, operative treatment.

MENINGEAL INJURY

Injury or violation of the meninges rarely occurs without violation of the skull. Bridging veins from the pial surface of the brain to the dura and its venous structures are easily torn, resulting in subdural hematoma formation. As discussed earlier, violation of the dura, particularly at the cranial base, may include vascular structures or lead to CSF rhinorrhea or otorrhea.

About 5% of epidural hematomas occur in the posterior fossa. Because of the limited volume within this space in addition to its close proximity to the brain stem, treatment of any expanding lesion in the posterior fossa must be considered urgent. Bounded posteriorly and laterally by bone and superiorly by the tentorium cerebelli, expanding posterior fossa hematomas can rapidly cause tonsillar herniation and brain stem compression leading to coma and death.

This occurrence was confirmed in a landmark study by Seelig and colleagues, who reported that patients who underwent craniotomy and evacuation of subdural hematomas within 4 hours of injury had a significantly lower mortality rate than did those who received treatment after the 4-hour window (30% versus 90% mortality).

not be associated with loss of consciousness, amnestic periods and long-term higher cognitive deficits have been reported. In classic concussions (i.e., those associated with a "reversible" neurologic deficit and temporary loss of consciousness), it is theorized that there is temporary neurophysiologic perturbations within the reticular activating system. Although there are no grossly evident radiographic or neuropathologic lesions, neurochemical and ultrastructural changes have been observed.

Diffuse axonal injury (DAI) is the most severe form of diffuse brain injury. When the tensile strain from angular acceleration and deceleration forces act on the brain parenchyma, axons and small vessels tear. Characteristically, the head-injured patient presents with a low GCS score (3 to 8), but no gross neuroradiographic abnormalities are evident. Placement of an ICP monitor may reveal intracranial hypertension that may require intensive medical therapy over the following days (see Chapter 41).

Patients with DAI who remain comatose for greater than 24 hours after the initial injury tend to have a worse prognosis and, in comparison to other types of head injuries, survivors of DAI have the highest frequency of permanent neurologic disability.

Evaluation of the Head-Injured Patient

HISTORY

Appropriate care for the head-injured patient requires rapid recognition and triage of the central nervous system injury. At the time of initial resuscitation and primary survey, a brief, pertinent history should be obtained. Knowledge of the mechanism of injury may provide insight into the degree of intracranial injury. Reports by the paramedics or other prehospital personnel of initial neurologic status often prove useful. For example, the report of a transient improvement in mental status, the so-called lucid interval, prior to hospital arrival can be vital in estimating the degree and time of onset of secondary brain injury. In patients with multiple injuries, information about hypoxic or hypotensive episodes should be sought, as they may have a significant bearing on clinical outcome. When sedation or paralytic agents have been administered in the field, information about the prehospital neurologic examination can be crucial. Recent drug or alcohol use complicates the diagnosis of severe brain injury, and a brief history of these and other toxins should be sought. Reports of nausea, vomiting, headache, and seizure-like activity are also critical to note.

PHYSICAL EXAMINATION

During the general examination, evaluation of the head and face for obvious external injury is important. If intracranial injury is suspected, the head should be maintained at a 30-degree elevation to reduce ICP and the neck should be supported with a cervical collar until the extent of injury is fully assessed. The skull should be inspected thoroughly to determine the presence and type (compound, open, or depressed) of fractures. Displacing fractures that cross major venous sinuses can cause severe hemorrhage and require urgent attention. Fractures of the orbital and maxillofacial structures often create distortion of facial anatomy. Bruising over the mastoid bone (Battle's sign), hemotympanum, and "raccoon's eyes" all suggest a basilar skull fracture. Careful inspection of the external ear canal and nares should be performed to assess for CSF leakage.

Teasdale and Jennett developed the GCS in 1974 as an objective measure of the level of consciousness after TBI. It has since become the most widely used clinical measure of the severity of TBI. It allows for a reliable and reproducible method of reporting ongoing neurologic evaluations by a variety of health care providers. The GCS evaluates eye opening, motor response, and verbal response (see Table 99.E1). This assessment tool, however, can be affected by reversible conditions such as hypoglycemia or narcotic overdose, as well as physiologic parameters such as hypoxia and

Unlike concussive syndromes, DAI is evident histologically throughout the callosal, periventricular, internal capsular, basal ganglia, and brain stem white matter. Tissue tear hemorrhages can occasionally be appreciated on the presenting computed tomographic scan. In fact, a grading system based on initial computed tomography (CT) results has demonstrated a correlation between computed tomographic severity of DAI and clinical outcome. When no intraparenchymal hemorrhage is present, T2-weighted magnetic resonance imaging typically demonstrates multifocal and hyperintense foci in the deep white matter structures. In postmortem studies, histologic evaluation reveals evidence of axonal injury and white matter tract disruption. Ultrastructural and immunohistochemical investigations have revealed several different mechanisms of axonal injury all culminating in irreversible disruption of the structural integrity of the axons.

hypotension. Therefore, the airway, breathing, and circulation should be assessed and stabilized prior to measuring the GCS.

In general, the GCS correlates with the severity of injury and relative prognosis of the head-injured patient. A patient who is awake and neurologically intact on presentation receives the highest score of 15. A neurologically devastated individual in flaccid coma receives the lowest score of 3. Mild TBI is usually considered to be a GCS of 13 to 15 and accounts for the majority of head injuries that present to the emergency room. Moderate injury falls in the 9 to 12 range, whereas a score less than 8 is indicative of coma. Confounding variables such as time between injury and assessment, interexaminer differences, body temperature, the presence of central nervous system depressants (such as alcohol), or hypotension at the time of presentation may all result in an inaccurate assessment of the severity and prognosis of the head injury.

Of equal importance to the GCS in establishing the severity of the injury is the recognition of both focal and global signs of neural injury. For example, careful examination of the pupil size and response to light is critical in the initial examination. A dilated, nonreactive pupil ("blown pupil") is the hallmark of life-threatening transtentorial herniation of the medial temporal lobe structures and indicates pressure on the ipsilateral third cranial nerve by an expanding intracranial lesion. In addition, compression of the cerebral peduncle directly by the temporal lobe results in contralateral hemiparesis.

Ocular movements are another important index of brain stem function. In states of depressed mental status, voluntary eye movements are compromised and oculocephalic or oculovestibular responses are used to determine the presence or absence of eye-movement disorders.

Signs and symptoms of *posterior fossa lesions* include agitation, headache, vomiting, hypotonia, dysmetria, and nystagmus. The patient may rapidly deteriorate to cardiorespiratory instability, coma, and death as an expanding lesion exerts pressure on the lower brain stem. Bilateral abnormal pupils can indicate severe brain stem injury, especially in the presence of obtundation or long tract signs. Any history of neuromuscular blockade, central nervous system depressants, or toxin exposure may confound the examination and should be sought. Finally, bilateral limb weakness, a defined sensory level, and bowel or bladder dysfunction are characteristics of a spinal cord injury and should be evaluated in any head-injured patient.

RADIOGRAPHIC IMAGING

Computed Tomography

With the availability and the rapid speed of spiral CT scanners, plain skull radiographs rarely provide any additional, relevant information in an acutely head-injured patient and are unwarranted. Most clinicians would agree that computed tomographic evaluation of the head is the most essential tool in the rapid diagnosis and delivery of care to the head-injured patient. This imaging technique accurately represents both soft tissue and bone trauma, and it specifically displays acute intracranial hemorrhage better than other radiographic modalities. The high sensitivity of CT to rule out acute intracranial pathology in mildly head-injured patients should make most clinicians have a low threshold to rapidly obtain such imaging in this population.

Furthermore, CT can identify skull fractures including those of the skull base and face. As mentioned previously, however, basilar skull fractures, when small, may not be readily apparent even with CT imaging, and if there is a high suspicion for such a lesion, the diagnosis must be made on clinical grounds. Foreign objects and their relationship to vital neural or vascular structures are also readily appreciated. With regard to high-velocity missile injuries, CT often displays the bullet's intracranial trajectory and the relative involvement of hemispheres, multiple lobes, ventricular system, or a combination. Also readily visualized are traumatic communications between cranial sinuses, the middle and inner ear compartments, and orbital or globe injuries. Pneumocephalus on the presenting computed tomographic scan is usually obvious and is pathognomonic of a skull fracture.

A Kernohan notch syndrome occurs when the contralateral third cranial nerve and peduncle are forced against the tentorial edge, causing a contralateral dilated pupil and ipsilateral hemiparesis. Because acute uncal herniation is accompanied by changes in mental status, the awake and otherwise neurologically intact patient with pupillary irregularities is likely to have a direct ocular injury. In contrast, in the stuporous or obtunded patient with these ocular findings, primary ocular injuries should be considered only after intracranial pathology has been ruled out.

Angiography

Either conventional digital subtraction angiography or CT angiography is indicated when vascular injury is suspected. For example, traumatic carotid artery dissection, pseudoaneurysm, and arteriovenous fistula are often related to skull base fractures.

Magnetic Resonance Imaging (MRI)

Although noncontrast head CT scan remains the imaging modality of choice in acute head trauma, MRI is a valuable tool to assess the extent of brain injury and determine further rehabilitation and treatment options. MRI is the preferred imaging modality in the diagnosis of diffuse axonal injury (DAI), particularly with gradient-echo sequences. MRI can play an important role in predicting the length of coma in DAI patients. However, MRI scanning is limited by the longer time to perform, limited accessibility, and inability to perform in the presence of metallic objects, including shrapnel and bullets.

Initial Management of the Head-Injured Patient

PRIMARY AND SECONDARY INJURY PREVENTION

All patients with severe head injury require the early consultation of a neurosurgeon. A deteriorating level of consciousness, uncontrollable hemorrhage, or lateralizing neurologic findings corroborated by intracranial pathology on CT scan demand the immediate involvement of a neurosurgeon to determine if surgical decompression or evacuation of the lesion is warranted. In less seriously injured patients, clinical evaluation of the patient, along with CT scan findings, should guide management prior to neurosurgical evaluation.

Initial management of the head-injured patient begins in the field or emergency department. In addition to the routine hematologic and biochemical studies, patients with severe head injuries should undergo osmolality tests and tests of renal function, coagulation (given the risk of disseminated intravascular coagulopathy), and glucose measurements. Neuronal injury may result from initial brain trauma (*primary injury*) or as the result of indirect mechanisms (*secondary injury*), such as hypoxemia, hypotension, and cerebral edema. Injury may also occur as the result of associated conditions that caused the trauma, such as hypoglycemia or drug toxicity. The goal of resuscitation in TBI is to rapidly preserve cerebral perfusion while minimizing neuronal injury.

Hypoxemia and hypotension are known to be profoundly detrimental to both short- and long-term outcome. There is evidence to support that patients with suspected severe TBI should be monitored continuously to maintain > 90% arterial hemoglobin oxygen saturation and > 90 mm Hg systolic blood pressure. Airway management is critical in the comatose patient with persistently low oxygen saturation despite supplemental oxygen therapy. This supports the use of endotracheal intubation in patients with GCS < 9.

Hemorrhage following brain trauma can profoundly decrease cardiac preload and compromise both central and peripheral perfusion and oxygen delivery. Aggressive intravenous fluid resuscitation is essential to support cardiovascular function. It has been well characterized that decreased cerebral perfusion can increase the extent of primary neurologic injury. The recommendation for adults is to rapidly infuse 20–30 mL/kg of Ringer's lactate or normal saline as an initial fluid bolus. Other options include using hyperoncotic and hypertonic fluids, as well as hemoglobin substitutes, but their routine use is not yet standardized.

Management of patients with TBI is directed at maintaining cerebral perfusion. Signs of cerebral herniation include dilated or unreactive pupil(s), asymmetric pupils, extensor posturing, or progressive neurologic deterioration, defined as a decrease in the GCS of more than 2 points from the patient's prior best score in patients with an initial GCS of less than 9.

ICP MANAGEMENT

Hyperventilation is beneficial in the immediate management of patients demonstrating signs of elevated ICP and cerebral herniation, but it is not recommended as a prophylactic measure because its effects cause cerebral vasoconstriction, thereby further compromising cerebral perfusion and potentially worsening the ischemia. Hyperventilation is administered as 20 breaths per minute in an adult with a goal end-tidal CO_2 of 30 to 35 mm Hg. Capnography is the preferred method for monitoring ventilation. If hyperventilation is used, patients should be assessed frequently for clinical signs of cerebral herniation.

Mannitol is also widely used to decrease ICP following TBI. It can be used both as a single bolus administration to control ICP while obtaining diagnostic information or planning for interventions, as well as a prolonged therapy for persistently elevated ICP. There is still controversy regarding the exact mechanisms by which mannitol exerts its therapeutic effect.

Mannitol therapy does, however, pose the risk of further reducing cerebral perfusion by lowering blood pressure. Hypertonic saline solutions are used as an alternative for lowering ICP in patients with TBI while preserving hemodynamic parameters. The mechanism of ICP reduction by hypertonic saline is thought to be due to mobilization of water across the blood-brain barrier, reducing cerebral water content. Hypertonic saline also dehydrates endothelial cells and erythrocytes, which increases the diameter of the cerebral vessels and deformability of erythrocytes, leading to plasma volume expansion with improved blood flow. Hypertonic saline infusion carries the risk of central pontine myelinolysis when given to patients with preexisting chronic hyponatremia and therefore plasma sodium levels should be checked prior to administration. Finally, hypertonic saline may also induce or aggravate pulmonary edema in patients with underlying cardiac or pulmonary problems.

Uncontrolled pain and agitation in TBI patients may contribute to dangerous elevations in ICP, raises in blood pressure, body temperature elevations, and resistance to controlled ventilation. Aggressive measures to reverse these factors should be undertaken. High-dose barbiturates were commonly used to lower ICP in the past. The mechanism of action of barbiturates has been attributed to coupling cerebral blood flow (CBF) to regional metabolic demands, thereby decreasing CBF and cerebral metabolic demands and lowering ICP. High-dose barbiturate therapy (so-called barbiturate coma), however, has shown no clear benefit in improving outcome.

SEIZURE MANAGEMENT

Posttraumatic seizures are common in TBI patients and vary in incidence from 4% to 25% for early seizures (occurring within 7 days from injury) and 9% to 42% for late seizures. It is important to prevent seizures in the acute period after TBI because they may contribute to elevations in ICP, blood pressure changes, and changes in oxygen delivery, and they may also cause excess neurotransmitter release. However, anticonvulsants have been associated with adverse side effects including fever, rashes, Stevens-Johnson syndrome, hematologic abnormalities, ataxia, and neurobehavioral side effects. Current guidelines do not support the use of prophylactic anticonvulsants for the prevention of late posttraumatic seizures. Phenytoin has been shown to reduce the incidence of early posttraumatic seizures in high-risk patients (GCS < 10, cortical contusion, depressed skull fracture, subdural or epidural hematoma, intracerebral hematoma, penetrating head wound, or seizure within 24 hours of injury). Therefore, it is common practice to empirically treat such patients with a 1-week course of phenytoin.

STEROID USE IN TBI

Steroids are commonly used in neurosurgical procedures for their effects of restoring altered vascular permeability in intracranial vasogenic edema, reducing CSF production, and attenuating

free radical production. In 2004, the collaborators of the Corticosteroid Randomization After Significant Head Injury (CRASH) trial reported the results of an international randomized controlled trial of methylprednisolone in patients with TBI. For this study, 10,008 patients from 239 hospitals in 49 countries were randomized to receive either 2 g IV methylprednisolone followed by 0.4 mg/h for 48 h, or placebo. The data-monitoring committee halted the study when interim analysis showed an increase in 2-week mortality in the steroid group versus controls (21% versus 18%). The mechanism of increased mortality with steroids in head-injured patients is still unclear, but steroids are currently not recommended in management of patients with TBI.

ICP MONITORING

There is a large body of published data that supports invasive ICP monitoring in severe TBI patients to help reduce mortality and morbidity. The purpose of intensive intracranial monitoring is to ensure adequate cerebral perfusion and oxygenation and avoid secondary injury. Cerebral perfusion pressure (CPP), an indirect measure of cerebral perfusion, relies on accurate assessment of mean arterial blood pressure and ICP. In addition, prophylactic treatment of ICP without ICP monitoring is not without risk. Therefore, ICP data are useful for prognosis and in guiding therapy, and there is an improvement in outcomes in those patients who respond to ICP-lowering therapies.

If ICP monitoring is considered, treatment thresholds need to be defined. The largest study using prospectively collected, observational data, controlling for a large number of confounding prognostic variables, analyzed the mean ICP in 5 mm Hg steps against outcome in a logistic regression model and found 20 mm Hg to have the optimal predictive value. However, it is known that patients can herniate at ICPs less than 20 to 25 mm Hg. The likelihood of herniation depends on the location and extent of injury of an intracranial mass lesion. Therefore, any chosen ICP threshold must be closely and repeatedly corroborated with the clinical exam and CT imaging in an individual patient.

In addition to ICP monitoring, preventing secondary brain injury requires adequate oxygen and metabolic substrate delivery to the brain. Delivery of oxygen to the brain is a function of the oxygen content of the blood and the cerebral blood flow. Delivery of glucose and other metabolic substrates to the brain also depends on CBF. Technologies used to measure CBF include Xenon-CT, positron emission tomography studies of CBF, and others. These advanced imaging techniques, however, remain uncommonly used in clinical practice because of expense and lack of expertise in performing and interpreting results. Other invasive monitoring devices have also been developed to measure CBF directly, including thermal diffusion probes, transcranial Doppler, jugular venous saturation monitors, brain tissue oxygen monitors, near-infrared spectroscopy, and cerebral microdialysis.

Outcomes

Outcomes correlate with a variety of factors, including mechanism of injury, examination on presentation, age, hypotension, anoxia, head CT results, level of ICP, timing of delivery of care, and the neurotrauma experience of the hospital. As a result, no gold standard for brain injury prognosis exists.

A standard instrument, the Glasgow Outcome Scale (GOS) (Table 99.1), was initially developed to describe the outcome of patients with head injury. In the GOS, patients are scored based on their level of disability, and, in general, the GOS correlates with the GCS.

Head injury has an overall mortality of approximately 14%, with many more patients having posttraumatic disability as measured by functional independent measures. The morbidity and mortality resulting from head trauma continue to tax the medical, financial, and social structure

CEREBRAL BLOOD FLOW AND OXYGENATION MONITORING

Jugular venous oxygen saturation monitoring in patients with severe TBI has shown that many patients experience episodes of desaturation due to both systemic (hypotension, hypoxia, hypocarbia, anemia) and cerebral (elevated ICP, vasospasm) causes. The frequency and severity of these episodes are associated with increased morbidity and mortality. In contrast, patients with elevated jugular venous oxygen saturation (SjO2) > 74% were found to have worse outcomes compared to patients whose mean SjO2 was 56% to 74%. This is thought to be secondary to poor tissue extraction of oxygen due to infarction or hyperemia.

Decreased brain tissue oxygen tension (PbO_2) has also been associated with increased morbidity in severe TBI patients. In 2005, Stiefel et al reported on a series of 53 patients with severe TBI treated with both standard ICP and CPP treatment goals (ICP < 20 mm Hg, CPP > 60 mm Hg) and the addition of an oxygen-directed therapy protocol aimed at maintaining $PbrO_2$ greater than 25 mm Hg. After comparing mortality and outcome at discharge with historical controls, they found a significant decrease in mortality (44% to 25%) in those treated with an oxygen-directed therapy protocol. Brain tissue oxygen tension monitoring reflects local changes in cerebral oxygenation, whereas jugular venous saturation is a surrogate for monitoring hemispheric cerebral oxygen extraction. Although jugular venous saturation monitors and brain tissue oxygen monitors hold promise in advancing the care of severe TBI patients, their use is not currently standardized at all tertiary care trauma centers.

TABLE 99.1 ■ **Scoring for the Glasgow Outcome Scale**

Outcome	Function	Score
Good recovery	Normal life	5
Moderate disability	Disabled but independent for daily activities	4
Severe disability	Dependent for daily activities	3
Persistent vegetative state	Unresponsive and bedridden	2
Death		1

of society. Early recognition, triage, rapid delivery of care, and a systematic, multidisciplinary approach to the trauma patient at designated trauma centers have been major advances in treating patients with acute head injuries. Furthermore, as the pathophysiology and molecular mechanisms of secondary brain injury are better understood, hypothesis-driven treatments can be tested. However, improved understanding of the myriad variables that affect outcome should not diminish educational efforts to modify behaviors to prevent head trauma in the first place.

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CHAPTER 100

Thoracic Trauma

John C. Kucharczuk ■ Jeffrey E. Cohen

The initial management of thoracic trauma should be identical to that of other traumatic injuries: rapid evaluation of airway, breathing, and circulation followed by a secondary assessment of injuries as delineated in the Advanced Trauma Life Support (ATLS) guidelines (see Chapter 96). Patients presenting with trauma to the thorax, however, may require rapid interventions unique to the mechanism of injury such as chest tube thoracostomy or pericardiocentesis. Although these interventions are often performed only after radiographic imaging, patients presenting with thoracic trauma may require such a procedure before imaging can be obtained. A chest radiograph should be attained in the trauma bay as soon as possible and should be evaluated for pneumothorax, subcutaneous or mediastinal emphysema, diaphragmatic rupture, widened mediastinum, and foreign bodies. The primary and secondary surveys, along with the initial chest radiograph, are usually sufficient to guide the provider along a tri-directional decision tree: additional imaging, tube thoracostomy, or the operating room. This chapter discusses in greater detail the variety of injuries and interventions associated with blunt and penetrating thoracic trauma.

Scope of Injuries and Management

CHEST WALL INJURIES

Injuries to the chest wall include fractures of the ribs, sternum, clavicle, scapula, and flail chest. It is important to note that blunt chest wall trauma, as opposed to penetrating trauma, is often associated with more severe intrathoracic injuries. Blunt thoracic trauma causes injury by three distinct (often overlapping) mechanisms: deceleration, direct impact, and compression. Deceleration injuries damage the structures suspended within and adhered to the thorax, such as the heart, lungs, and aorta. Direct impact typically causes localized fractures of the ribs or sternum but can also damage the underlying heart or lungs. Compression injuries, similar to those caused by direct impact, can involve not only the surrounding thoracic wall but also, when severe enough, organs and vessels within. It is thus critical for the clinician to be cognizant of the fact that any trauma to the chest wall can be associated with much more severe *intra*thoracic damage.

The most common injury to the thorax is rib fracture. The diagnosis can usually be made by simply observing the patient's respiratory pattern and level of pain upon deep inspiration. The treatment of unilateral rib fractures is pain control. For multiple or bilateral fractures, a more aggressive and complex analgesic plan is usually required, often involving some form of neuraxial anesthetic (e.g., epidural catheter), paravertebral block, or intercostal nerve block (see Chapter 86).

When trauma causes a part of the chest wall to move separately from the surrounding bony structures, a paradoxical motion occurs with respiration known as "flail chest." The flail portion moves inward as the patient takes an active inspiratory effort. Flail chest can result from unilateral or bilateral rib fractures, or disruption of the costochondral junction. It is seen more commonly in elderly patients because of their reduced chest wall compliance. As a result of the discordance between the motion of the chest wall and the intrathoracic volume, there is decreased vital capacity and ineffective ventilation, which, when coupled with an underlying pulmonary contusion,

can result in the development of acute respiratory distress syndrome (ARDS). Early intervention, including pain control, humidification of air, and aggressive pulmonary toilet, is critical in order to avoid clinical deterioration. Arterial blood gases can be followed to evaluate the adequacy of ventilation and oxygenation over a short period of time. Non-invasive ventilation is often unsuccessful because the primary problem remains severe pain and discordant chest movement; however, obligatory intubation without evidence of respiratory failure is not recommended. If clinical improvement is not seen rapidly, elective mechanical ventilation should be considered. Mortality has improved significantly over the years from flail chest, but many patients suffer from long-term debilitation including dyspnea, abnormal exercise tests, and pain. In short, flail chest is a serious injury that must be managed early and aggressively.

Other fractures of the chest wall include those of the sternum, clavicle, and scapula. Sternal fractures are frequently secondary to motor vehicle crashes. Although imaging can be helpful, diagnosis can often be made by physical examination demonstrating point tenderness and sternal deformity. Myocardial injury is frequently associated with these fractures; however, the clinical significance varies by patient. The treatment of chest wall fractures is similar to that of rib fractures except in cases where the fracture is severely displaced. Such cases require operative intervention. Scapular fractures are rare but are almost always associated with concomitant injury, particularly within the brachial plexus. Treatment is mostly nonoperative, although there are specific fracture patterns that require an operation. There are no defined guidelines for surgical intervention of chest wall fractures. Therapy is typically individualized based on the fracture type and other comorbidities. Unlike scapular fractures, those of the clavicle are often isolated and have little clinical consequence.

LUNG AND MYOCARDIAL CONTUSION

Myocardial contusion is usually secondary to blunt chest trauma. Serum troponin levels, though not specific for contusion, are a sensitive indicator of myocardial injury. Patients with normal troponin levels, normal electrocardiogram, and no other significant injuries typically do not require hospital admission. Elevated troponin levels require admission and monitoring until they return to normal. Early sequelae of cardiac contusion include ventricular arrhythmia, ventricular wall rupture, septal rupture, valvular insufficiency, intracardiac thrombus formation, and laceration of coronary artery resulting in myocardial infarction. Manifestations of these complications typically occur within the first 24 to 48 hours after injury. Echocardiography is indicated when there is hemodynamic instability, a discrepancy between troponin levels and ECG findings, and when troponin levels continue to rise. In general, the treatment of myocardial contusion is supportive.

Pulmonary contusion can result from severe blunt chest wall trauma causing intraparenchymal hemorrhage and edema. It is usually apparent on the initial chest radiograph, though it may not become apparent until 24 to 48 hours after the initial injury. Indications for endotracheal intubation are similar to those of other chest trauma and should be guided by clinical judgment and arterial blood gas trends. Fluid restriction is appropriate in elderly patients and those with evidence of volume overload; however, not all pulmonary contusion patients warrant fluid restriction and diuresis. Massive contusions causing large intrapulmonary shunts with hypoxemia can be managed with a double-lumen endotracheal tube. It is important to distinguish a pulmonary hematoma from a contusion on initial chest film. After 24 to 48 hours, a hematoma will appear as a discrete mass on chest radiography or computed tomography (CT) scan and is usually of minor clinical consequence.

AORTIC DISRUPTION

Thoracic aortic injury usually results from rapid deceleration and is responsible for 10% to 15% of deaths following motor vehicle collision. Of these patients, about 90% will die before reaching the hospital. A high index of suspicion and careful inspection of the initial chest radiograph

are essential to making the diagnosis. Radiographic findings include a widened mediastinum, blurring of the aortic knob, loss of the normal anteroposterior window, a left apical cap, and depression of the left mainstem bronchus inferiorly. Although the sensitivity of chest radiography approaches 90% to 95%, the specificity is only 10%. Fortunately, advances in CT scanning have made this imaging modality the gold standard for diagnosis of aortic injury with a sensitivity of 100% and specificity of 80% to 85%. Additionally, the ability to perform three-dimensional reconstructions further aids in diagnosis and intervention. Other imaging modalities that can be helpful include magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and transesophageal echocardiography (TEE). Although immediate operative intervention was historically the only option, that is no longer the case. In patients who are hemodynamically stable, initial management involves beta-blocker therapy with a goal systolic blood pressure of less than 120 mm Hg. Although surgery is eventually required for most patients, endovascular stent grafts have become an attractive alternative to a more invasive procedure. Early data have shown lower rates of perioperative mortality and paralysis compared with open repair.

PNEUMOTHORAX AND AIR LEAKS

Pneumothorax is a relatively common occurrence in patients presenting with thoracic trauma. Unlike nontraumatic pneumothoraces, those caused by thoracic trauma should, in general, always be managed with chest tube thoracostomy. This is particularly important for patients who will require positive pressure ventilation. One exception is the finding of an *occult* pneumothorax, defined as one seen on CT but not on chest radiography. Occult pneumothoraces can often be safely managed with observation and high concentration of supplemental oxygen therapy.

A *tension* pneumothorax causes a shift in the mediastinal contents and often results in rapid respiratory and hemodynamic deterioration. Physical examination findings consistent with this diagnosis include respiratory distress, distended neck veins, deviated trachea, or absent breath sounds. Treatment involves immediate decompression and can be accomplished with placement of a 14G angiocatheter in the second intercostal space in the midclavicular line.

The presence of a large air leak or large amounts of subcutaneous emphysema must lead one to suspect a tracheobronchial or esophageal injury. Bronchoscopy should be performed following endotracheal intubation to better evaluate the airway. More than 80% of these injuries occur within 2.5 cm of the carina, and most are diagnosed late. Thus, a high index of suspicion is necessary in order to make the diagnosis. The traditional management of these injuries is early operative repair.

HEMOTHORAX

Hemothorax can occur as a result of both penetrating and blunt trauma. The goal of initial management is complete drainage of blood from the thoracic cavity, which can be accomplished with a large bore (32 Fr to 36 Fr) chest tube. ATLS guidelines are employed to determine whether thoracic exploration in the operating room is required. In general, an initial output from the chest tube of greater than 1500 mL of blood or greater than 250 mL/hour for the first 4 hours is an indication for surgical intervention. Typical sources of bleeding include the intercostal or internal mammary arteries, pulmonary lacerations, and great vessel injury. Any residual hemothorax should be evacuated to reduce the risk of empyema and fibrothorax. Although drainage is not an emergency, it should be performed within 24 to 72 hours of injury.

EMERGENCY DEPARTMENT THORACOTOMY

Emergency department thoracotomy (EDT) is a drastic measure with specific indications. Generally, it is performed in the setting of cardiopulmonary collapse secondary to penetrating thoracic

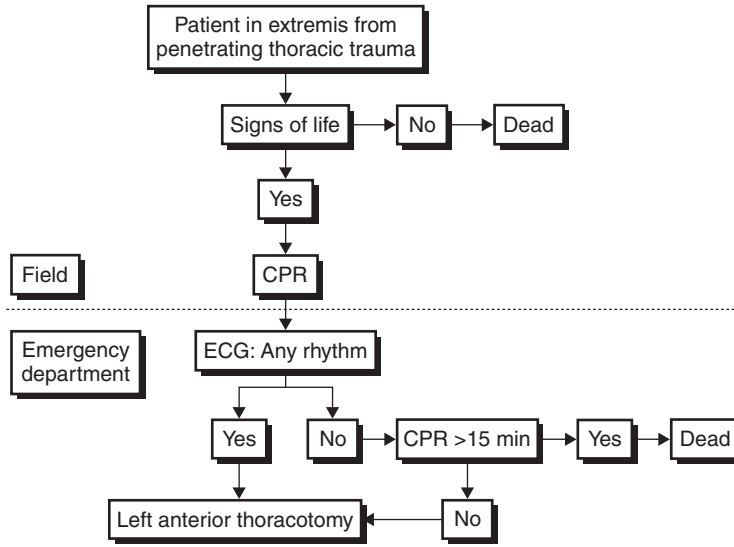


Figure 100.1 Schematic for emergency department thoracotomy (EDT). *(From Mollberg NM, Glenn C, John J, et al: Appropriate use of emergency department thoracotomy: implications for the thoracic surgeon. Ann Thorac Surg 92:455-461, 2011.)*

trauma. The recommended indication for EDT is a patient who sustains penetrating thoracic trauma with signs of life in the field and has received less than 15 minutes of CPR (Figure 100.1). If these criteria are not met, EDT is rarely indicated as it offers *no* benefit to patients and exposes health care personnel to potential risk. When indicated, the incision is usually made through the fourth intercostal space. The primary interventions are rapid control of bleeding, often necessitating cross clamping of the proximal descending thoracic aorta. The overall survival with neurologic function following EDT is approximately 5% to 10%; however, the mechanism of injury has been shown to affect outcome. In short, EDT is a drastic but potentially lifesaving maneuver when properly employed.

Complications in the Intensive Care Unit

AIR EMBOLISM

Arterial air embolism (AAE) occurs when air gains access to the pulmonary venous circulation. The incidence is between 4% and 14% in thoracic trauma. The mechanism usually involves injury to a bronchus near the hilum, close to the pulmonary venules, creating a fistulous connection between the airway and the pulmonary venous system. The proclivity for air to be entrained into the blood vessel is accentuated by positive pressure ventilation and hypovolemia. The typical clinical presentation includes hemoptysis, cardiovascular collapse, seizure, and livedo reticularis. This constellation is frequently associated with the institution of positive pressure ventilation. Transesophageal echocardiograph (TEE) can be useful to confirm the diagnosis. Treatment involves minimizing intrathoracic pressure and maintaining euvolemia. A double lumen endotracheal tube or endobronchial blocker can be utilized to ventilate the unaffected lung. Continued cardiovascular collapse warrants emergent thoracotomy to control the source of air.

UNDRAINED PLEURAL FLUID COLLECTIONS

Although small pleural fluid collections usually reabsorb uneventfully, moderate to large ones, if left untreated, can lead to empyema or fibrothorax. As a result, these collections should be drained with a chest tube and antibiotics started empirically if the fluid appears infected. If the collection is left undrained for too long, the pleural fluid may become gelatinous, necessitating more invasive means of drainage (e.g., video-assisted thoracoscopic surgery). If treatment is further delayed, a fibrous peel may form, entrapping the lung. In these cases, surgical decortication is the only option remaining.

BRONCHOPLEURAL FISTULA

A bronchopleural fistula (BPF) is defined as a direct communication between the pleural cavity and a lobar or segmental bronchus. This must be distinguished from an air leak originating from the lung parenchyma. Approximately 5% of patients undergoing lung resection for trauma will develop a BPF from surgical stump breakdown. The diagnosis is characterized by acute onset of tachypnea, purulent secretions, fever, subcutaneous emphysema, and rarely tension pneumothorax. Bronchoscopy can confirm the diagnosis. The goal in the management of BPF is to repair the leak. This is different from the management of parenchymal-pleural fistulas, which are primarily supportive. Initial intervention should be chest tube placement, minimizing positive pressure ventilation, and empiric antibiotics. Single lung ventilation may be necessary and peak airway pressures should be minimized. Advances in endoscopic techniques have made available endobronchial or pleural-based methods of sealing leaks as both a bridge to surgery and definitive repair.

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CHAPTER 101

Spinal Injury

Paul Marcotte ■ Andrew Freese ■ Uzma Samadani

The intensivist managing the patient with major trauma in the intensive care unit (ICU) setting must be vigilant for the presence of a coexistent injury to neural or osteoligamentous components of the spine. The history and neurologic examination determine the functional status and level of the neurologic injury, whereas imaging studies determine the integrity and stability of the osteoligamentous complex. Despite the advances of imaging investigations, plain films remain of value for defining instability, especially in the cervical spine. Computer-assisted imaging (computed tomography [CT]) and magnetic resonance imaging (MRI) are complementary studies, each of which contributes valuable information to the assessment and management of the patient with a spinal injury (Table 101.1).

Three goals guide the ICU management of patients with spinal injuries: (1) preventing neurologic injury or progression of an existing neurologic deficit, (2) enhancing the physiologic environment in which neurologic recovery takes place, and (3) stabilizing the spinal column. This chapter presents the management principles and the pharmacologic, nonsurgical, and surgical interventions used to achieve these goals.

Pathophysiology and Biomechanics of Spinal Injury

Spinal cord injury can be subdivided into primary and secondary injures. In the setting of trauma, the *primary injury* results from the application of force to the spinal cord, causing vascular injury or direct injury to the neuronal and non-neuronal cell populations. The severity of the primary spinal cord injury remains the strongest predictor of neurologic outcome.

Secondary spinal cord injury results from a cascade of physiologic and biochemical events that follow the primary injury. The cascade involves the formation of oxygen-free radicals, cell membrane disruption, and cell death. Factors such as ischemia and hypoxia can accelerate local metabolic injury, emphasizing the need for rigid control of systemic blood pressure and oxygenation in the management of a patient with a spinal cord injury.

The cervical spine (C-spine) consists of the atlantoaxial complex and the subaxial C-spine. The major articulation at the atlantoaxial complex involves the odontoid process and the anterior arch of C1, which is stabilized by the transverse ligament. Direct ligamentous injury and bony injuries that cause incompetence of the transverse ligament complex produce atlantoaxial instability. These include some C1 fractures, most odontoid fractures, transverse ligament injuries, and complex atlantoaxial fractures. Unstable subaxial C-spine injuries are diagnosed on lateral C-spine films obtained in a neutral position and during flexion and extension.

Unstable injuries of the thoracic spine are more likely to occur at the thoracolumbar junction or in the lumbar spine because of the stabilizing capabilities of the rib cage and sternum.

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TABLE 101.1 ■ **Imaging Studies for Spinal Injury**

Study	Advantages	Disadvantages
Plain radiograph	Performed rapidly as a portable study; can be used to determine stability in flexion and extension	Poor resolution
Computed tomography	Shows bony structure well, can be used to reconstruct cervicothoracic junction	Worse than magnetic resonance imaging for tissue densities; not portable
Magnetic resonance imaging	Excellent tissue definition (cord, ligament, hematomas)	Poor bone definition, not portable, more time required for study compared with computed tomography

Assessment of Spinal Cord Injury

The first priority with respect to managing any critically injured patient remains assessment and stabilization of the airway, breathing, and circulation. Unnecessary manipulation of the patient's spine, however, should be avoided before radiographic confirmation of stability.

Inspection of the body for superficial abrasions and contusions can assist in the differential diagnosis of the neurologic injury, localizing it either centrally or to the periphery. Palpation of the entire spine may provoke pain, which can assist in localization of the level of a significant spinal injury. Pain, however, does not determine the extent and stability of the spinal injury. Any pain identified by manual examination requires imaging of that segment of the spine to assess for an osteoligamentous injury. On occasion, with extreme spinal trauma, widening of the interspinous space or step-offs between adjacent vertebrae can be appreciated by palpating posteriorly. Such findings occur rarely in isolation and patients with such findings often have severe neurologic deficit, localized pain, or both.

The primary purpose of the neurologic examination is to assess the integrity of peripheral neural function. A limited assessment of cognitive and cranial nerve function should be performed to determine the presence of intoxication, hypothermia, or brain injury as these processes can interfere with the interpretation of the examination of the peripheral nervous system. The presence of a *unilateral* neurologic deficit, except in the instance of penetrating spinal injury, is more typical of an intracranial abnormality or involvement of a peripheral nerve, or nerve root, or plexus. Acceleration and deceleration injuries of the spinal cord generally produce symmetric deficits.

A complete assessment of spinal cord function necessitates a thorough examination of sensory, motor, and reflex function. In particular, a segment-by-segment assessment of each dermatome and myotome must be made to determine the level and completeness of the spinal cord injury.

SENSORY EXAMINATION

The sensory examination should include assessment of both pain perception and proprioception as these two modalities travel through distinct anatomic tracts in the spinal cord (spinothalamic tracts and posterior columns, respectively). Appreciation of noxious stimulus requires a dermatome-by-dermatome assessment from the highest cervical to the lower sacral levels (Figure 101.1).

The lower cervical and upper thoracic dermatomes (C5-T2) are not represented on the anterior torso. The upper cervical dermatomes (C3-4) extend to the supramammary region, immediately superior to the T3-4 dermatome. Examination of the torso alone results in a sensory assessment that makes the transition from the C4 to the T4 levels, not directly testing the intervening

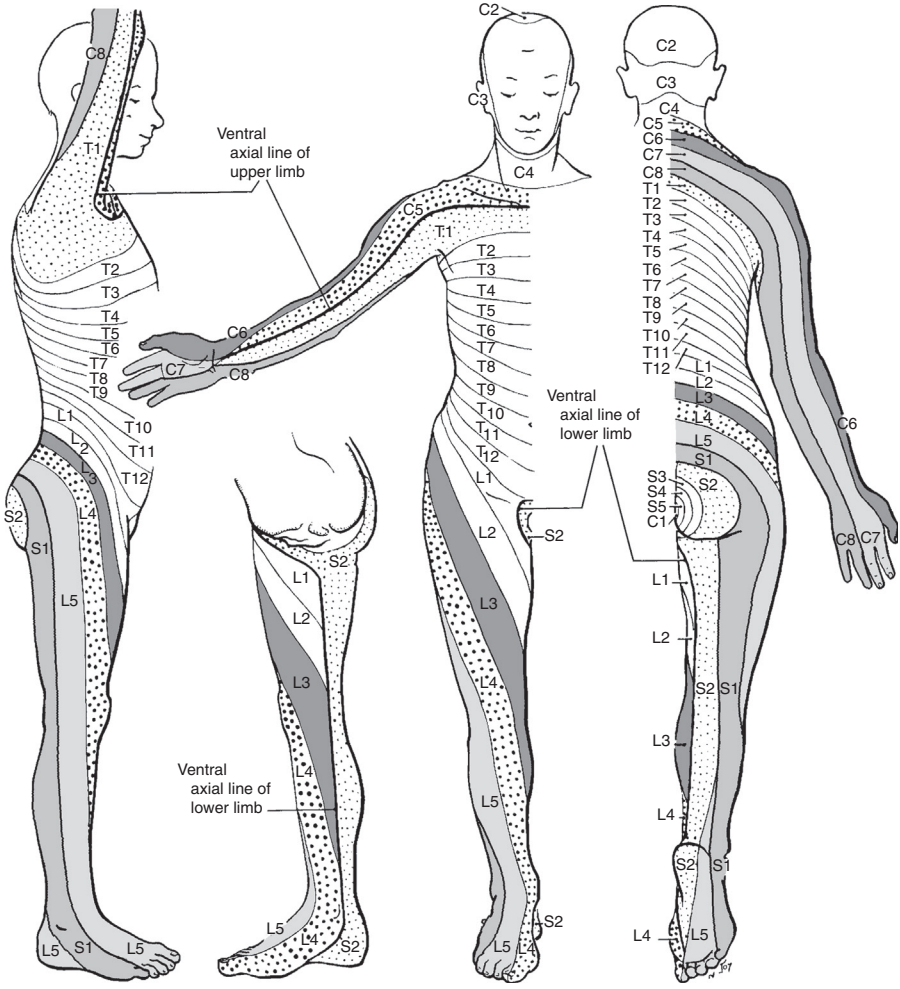


Figure 101.1 Typical location of dermatomes. When transmission via a dorsal nerve root is interrupted, the result is a diminution of sensation (pin prick, light touch, or temperature) in the associated dermatome. *(From Grant JCB: Grant's Atlas of Anatomy, 5th ed. Baltimore: Williams & Wilkins, 1962.)*

dermatomes. For this reason, a detailed examination must be carried out in the arms and hands to assess these areas. Otherwise, a patient with a low cervical injury can be misdiagnosed as having an upper thoracic injury by a sensory assessment limited to the torso.

The upper extremity sensory assessment must include all six dermatomes represented on the arm for adequate localization of a deficit. Individual leg dermatomes should also be assessed, although disparity in sensory function in a dermatomal pattern after a spinal cord injury is less common in the legs (see Figure 101.1).

The sacral dermatomes, located within the perineal region, should also be tested (see Figure 101.1). The presence of perineal sensation alone ("sacral sparing") in a patient who otherwise has no demonstrable neurologic function represents an incomplete spinal cord injury, which may have a better prognosis for recovery of spinal cord function than can be expected in a patient with a complete injury.

The assessment of posterior column function involves position and vibration sense testing. Because pain and proprioceptive fibers travel within the same peripheral sensory nerves, posterior column testing can involve the distal aspects of the upper and lower extremities alone, after the detailed noxious stimulus assessment. A disparity in the results of sensory assessments between proprioceptive and pain appreciation occurs only in a patient with a partial cord injury affecting either the posterior or anterior aspects of the cord alone. Transverse injury, or an injury involving a peripheral nerve, should affect spinothalamic and posterior tracts with equal severity.

MOTOR EXAMINATION

Like the sensory examination, the motor examination must be meticulously performed, assessing individual myotomes of the upper and lower extremities. Proximal arm and forearm motion observed by a cursory examination can obscure the presence of a lower cervical injury involving the triceps and intrinsic hand functions. In the lower extremities, thoracic spinal cord compression can manifest itself as proximal motor weakness in the legs with sparing of distal muscle groups.

REFLEX EXAMINATION

The reflex examination includes deep and superficial reflex assessments. The deep tendon reflexes are tested in the arms and legs. The significance of abnormal reflexes depends on the location and time course of the injury.

In the presence of an acute complete spinal cord injury, the deep tendon reflexes below the level of the lesion are hypoactive. In some instances, normal reflex activity may be seen in the hyperacute state. Hyperactive reflexes develop in the subacute phase (4 to 6 weeks) after an injury because of the loss of inhibition from descending corticospinal pathways. The Babinski reflexes follow the time course of the deep tendon reflexes. In the acute phase of an injury to the spinal cord, they remain unreactive, or a flexor response is occasionally identified. Extensor plantar response develops from chronic compression of the spinal cord or in the subacute phase of an injury.

In acute trauma, the differential diagnosis of hypoactive reflexes includes nerve root injury, plexus injury, and spinal shock. The underlying cause of hyporeflexia is determined by the pattern of the patient's neurologic symptoms and associated motor and sensory deficits. In addition, hypoactive reflexes may be due to a preexisting condition such as peripheral neuropathy or chemotherapy use, or they may be a normal variant.

Focal hypoactive reflexes in the *upper extremities* are often the result of a nerve root or brachial plexus abnormality. If the motor and sensory deficits correspond to multiple, adjacent motor or sensory root levels, a plexus injury is likely the underlying cause. Contusions or abrasions of the skin, or underlying fractures involving the shoulder girdle structures, pelvis, or transverse processes, can be associated with these deficits, and their presence should be sought to confirm the diagnosis.

Spinal shock is a phenomenon that is present after a complete spinal cord injury. The patient has absence of all volitional and reflex neurologic activity below the level of the lesion. In contrast, *neurogenic shock* is a hemodynamic phenomenon. After spinal cord injury at or above the T5 vertebral level, patients may become hypotensive. Characteristically, patients have a relative bradycardia in the presence of low blood pressure. The shock results from the loss of sympathetic outflow. This causes peripheral vasodilation and pooling of blood, which, in turn, impairs venous return to the heart. Loss of sympathetic outflow also has negative inotropic and chronotropic effects on the heart.

Superficial reflexes are diminished in the presence of a spinal cord injury. Nerves from T6-9 and T10-12 subserve the upper and lower superficial abdominal reflexes, respectively. The absence of both upper and lower superficial abdominal reflexes indicates that the lesion is above T6. The absence of lower and preservation of upper superficial abdominal reflexes indicates that the lesion is below T9. Likewise, the L1-2 segmental nerves mediate the cremasteric reflex, and loss of this reflex is pathologic.

The tone of the anal sphincter should also be assessed as part of a full neurologic workup. It is usually diminished or absent in the presence of a complete acute spinal cord injury.

RADIOGRAPHIC EXAMINATION

Indications for spinal imaging (see Table 101.1) include (1) history of trauma, (2) neurologic deficit, (3) local spinal tenderness, and (4) a nonresponsive or unconscious patient. Imaging is performed to determine the integrity of the osteoligamentous complex, assess the presence and cause of ongoing neural compression, and determine the optimal surgical approach to a spinal lesion.

Despite advances in computer-assisted imaging, plain radiographs remain an integral part of the imaging assessment of the spine. They are particularly useful in the ICU setting because portable radiographs are readily available, requiring little manipulation or transportation of the patient. Plain radiographs give an initial indication of the potential for osteoligamentous injury. In particular, lateral radiographs are essential because the criteria for determining stability of a spinal segment are based on these projections, particularly in the C-spine.

Management

STABILIZATION OF THE INJURED SPINE

When the mechanism of injury to a patient is consistent with a possible spinal injury, the spine is stabilized while cardiorespiratory resuscitation is undertaken.

Immobilization of the spine in a neutral position generally protects the neural elements from further injury in the presence of an unstable injury. Protection of the cervical spine often begins in the field during transportation of an injured patient. Techniques include application of a rigid cervical collar or immobilization of the head and torso on a rigid spinal board with lateral props, such as sandbags or rigid foam inserts. If the head is fixed to the backboard, the rest of the patient's body should be rigidly secured to the board. This approach to stabilization should be viewed as temporary because an unconscious or spine-injured patient who has lost sensation can quickly develop pressure ulcers if left immobilized on a rigid backboard even for only a few hours.

Although a cervical collar is adequate for a cooperative, calm patient, it is insufficient for an uncooperative, active patient with a potentially unstable cervical spine. An effective alternative in the ICU is cervical traction. Traction is useful for realigning the spine, and it protects against movement that could compromise the spinal canal. Patients in traction should be carefully followed by serial cervical spine films and neurologic examinations. Cervical traction is inappropriate, however, for patients with unstable atlantoaxial injuries. Instead, they should be placed in a cervical collar or a halo ring and vest. The vest, however, is less effective than the halo ring at maintaining the stability of the cervicothoracic junction.

In some circumstances, the halo ring and vest can be impediments to the care of the ICU patient. They restrict access for central line placement, chest tube placement, airway management, and cardiac compression. The instrument required for removal of the halo should be readily accessible and accompany the patient at all times. If appropriate and necessary, traction can be a temporary alternative.

There are fewer good techniques for immobilization of the thoracolumbar spine. Backboard positioning is first initiated empirically in the field. Subsequently, if the patient is relatively immobile on a standard mattress, he or she is unlikely to incur further neurologic injury. Firm mattresses are preferable to soft ones. A thoracolumbosacral orthosis or cast enhances immobilization and prevents flexion in an uncooperative patient.

Thoracolumbar traction is more cumbersome and is less effective for reducing deformity, and halo-pelvic traction is rarely used.

A complete C-spine study includes a view incorporating the occiput to the C7-T1 junction. The shoulders can obscure the cervicothoracic junction. Techniques available in the ICU to augment visualization of this region include manual downward traction on the arms and a swimmer's view. If the junction cannot be seen adequately despite these supplementary techniques, computer-assisted imaging is required. Plain cervical radiographs in flexion and extension enable dynamic imaging for the assessment of stability. These views can be obtained in the ICU with plain films for a conscious, cooperative patient or with fluoroscopy in an unconscious patient. Because there is a 5% frequency of noncontiguous spinal fractures in trauma patients, visualization of the entire spine must be obtained in the presence of trauma, even if an unstable injury is found at one segment of the spine.

NONOPERATIVE TREATMENT

In the presence of an existing neurologic deficit, there are limited means of augmenting neurologic recovery. General care of the patient, including maintaining blood pressure, oxygenation, and nutrition, provides an environment in which neurologic recovery can potentially take place and may contribute to the prevention of progressive secondary spinal cord injury. Also, it is important to identify and treat related medical complications associated with a spinal cord injury, which can be life threatening and increase morbidity and the duration of in-hospital recovery.

Pharmacologic means of augmenting spinal cord recovery are under active investigation. The use of high-dose steroids has demonstrated some efficacy for acute spinal cord injury. The National Acute Spinal Cord Injury Study II assessed the benefits of steroid administration after spinal cord injury. It had two treatment arms and a placebo group. One treatment group received high-dose methylprednisolone (30 mg/kg intravenous bolus over the first hour, followed by 5.4 mg/kg/h of a continuous infusion over the subsequent 23 hours), and the other treatment group received naloxone. When the steroids were given at these doses within 8 hours after the injury, a statistically significant improvement in neurologic outcome without increased morbidity was found. The neurologic outcome with naloxone was found to be the same as with placebo.

In view of these results, most agree that a patient presenting with a partial spinal cord injury within 8 hours of the injury should receive high-dose methylprednisolone. The merits of high-dose steroids in a setting of a complete spinal cord injury are less certain, although some also advocate their use in this situation.

In the ICU, nonoperative techniques are usually sufficient to stabilize an injured spinal segment. Postural reduction or segmental immobilization with collars and braces is usually sufficient in a noncombative patient to prevent induction or progression of a spinal cord injury. The priority in the ICU setting should be to stabilize the patient's cardiorespiratory function and treat other acute medical conditions. Because nonoperative techniques can be used to stabilize osteoligamentous injuries, definitive treatment should be undertaken on an elective basis.

OPERATIVE TREATMENT

In contrast to the limitations in enhancing neurologic recovery after spinal cord injury, techniques for spinal stabilization have greatly improved. As a result, except for some atlantoaxial injuries, most unstable spinal injuries are treated operatively.

The principles of spinal surgery, regardless of cause, include decompression, reduction, and stabilization. These principles are most clearly illustrated in the setting of acute trauma.

Decompression

Spinal cord compression results from retropulsion of bone or soft tissue (disk, hematoma) into the spinal canal. The effectiveness of acute or subacute spinal cord decompression after the initial spinal injury is controversial. Most would agree that the effect of compression on the neural elements is maximal at the time of impact. During this interval, the compressive fragment or spinal translation occurs with the encroaching element being accelerated into the spinal cord, thereby imparting force on the neural elements.



One clear indication for emergent spinal cord decompression is a patient who has progressive neurologic deficit and ongoing neural element compression. Decompression of a patient with a complete deficit is considered elective and some would deem it unnecessary. The patient with a stable, partial cord deficit could be considered for a neural decompressive procedure at the time of definitive stabilization. Reports of clinical improvement in groups of patients who have chronic deficits after delayed spinal cord decompressions indicate the potential merits of neural element decompression.

It is uncertain if the ongoing compression after the initial impact continues to promote injury via a primary or secondary mechanism. Theoretically, the presence of ongoing compression could increase local tissue pressure and thereby alter regional perfusion, promoting secondary injury. Those authors who advocate early decompression cite this theoretic concern.

Others recommend elective, delayed decompression based on the concern of incurring a secondary injury at the time of surgery—for example, operating on a patient who is unstable from a cardiac or respiratory point of view. With refined operative techniques, including anterior approaches, and advances in neuroanesthesia, early intervention for decompression has become safer and its efficacy is being reevaluated.

Reduction and Stabilization

Depending on the nature of the injury and the segment of the spine involved, reduction can be performed by external or internal techniques. Although cervical traction is effective for realigning translational deformity in the cervical spine, thoracolumbar traction is relatively ineffective. Open, internal reduction is feasible along all segments of the spine. To achieve reduction, a force must be applied to the spine to counteract the deforming force and to prevent subsequent deformity after the initial reduction.

Stabilization of the spine must be considered in terms of immediate and long-term stability. In the setting of acute trauma, immediate stabilization is provided by application of a rigid immobilizing device, either internally or externally. Bony healing or fusion will achieve long-term stabilization.

Venous Thromboembolism Prophylaxis

Patients with spinal cord injury have a very high, but variable risk of developing deep venous thrombosis (DVT). This variability primarily depends on the timing and choice of antithrombotic prophylaxis as well as the extent and level of cord injury. Without prophylaxis, the incidence of DVT in patients with acute spinal cord injury (SCI) is approximately 40%. Although prophylactic therapies have the potential to reduce the incidence tremendously, the risk is not eliminated. It is also apparent that depending on the particular level of cord injury, patients have different risks for developing venous thromboembolism (VTE). In a retrospective study of more than 18,000 patients with spinal cord injury, patients who sustained injury to a high thoracic level (T1-6) were found to have a high rate of VTE (6.3%), whereas those with high cervical injuries (C1-4) had a much lower rate (3.4%). Importantly, close to 10% of all deaths in the first 12 months after SCI are attributable to venous thromboses. Thus, strategies to prevent clot formation should be instituted early. Because early ambulation is frequently not an option for these patients, alternatives include pharmacologic anticoagulation, partial venous occlusion devices (i.e., filters), and antithromboembolic stockings. Of equal importance is the timing of such therapy. Although data on the timing of initiation remain somewhat equivocal, most agree that therapy should be initiated as early as possible and no later than 72 hours after injury if possible. Accruing data affirm and guidelines now recommend low-molecular-weight heparin (in particular, enoxaparin) over either standard or unfractionated heparin for the prevention of VTE in patients who have sustained spinal cord injury. Compression stockings, though helpful, should only be used as an adjunct to appropriate pharmacologic therapy. Finally, even though the prophylactic placement of caval filters in SCI patients acutely may seem theoretically appealing, data have not supported this practice and current guidelines do not recommend their placement routinely. Placement of a filter may be warranted in patients who are unable to receive pharmacologic anticoagulation but the long-term complications of such a procedure must be considered.

An annotated bibliography can be found at www.expertconsult.com.

Significant innovations have been made in the development of internal fixation devices. The purpose of such spinal instrumentation is to achieve short-term fixation of the spine and, in some cases, deformity correction. In addition to stabilizing the involved segment of the spine, some devices have dynamic properties that enable the application of force to the spine for deformity correction. A major advantage of this type of instrumentation is that it achieves immediate stabilization of the spine. The patient is able to commence physical and rehabilitation therapy without risking neurologic injury. Early rehabilitation reduces the likelihood of complications that can result from prolonged recumbency. The disadvantages of a fixation device include added operative time and risk, immobilization of segments with normal motion in order to achieve adequate fixation, and imaging artifact obscuring anatomic detail on postoperative studies.

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CHAPTER 102

Ethical Principles, Communication, and End-of-Life Care

Joshua B. Kayser ■ Paul N. Lanken ■ Horace M. DeLisser

Death is common in intensive care units (ICUs). Approximately 20% of deaths in the United States occur in ICUs, and 50% of patients dying in a hospital spend at least some of their hospitalization time in an ICU. Although the majority of these deaths in ICUs involve the withholding or withdrawal of life-sustaining therapy, few of these patients have the capacity to make decisions regarding goals of care and the limitation of life-prolonging therapies. Likewise, only a small percentage of patients have completed an advance directive that might aid surrogates and physicians in the decision-making process. Many decisions about end of life in the ICU are therefore made without the patient's direct involvement or input. This chapter describes the principles of medical ethics as applied to end-of-life decision making and care for ICU patients.

Basic Principles (Values) of Medical Ethics

The basic principles (or values) of medical ethics (Figure 102.1) speak to the rights of patients (autonomy), the duties of physicians (beneficence and nonmaleficence), and societal concerns for fairness in the allocation of medical resources (distributive justice).

Rights of the Patient

PATIENT AUTONOMY DEFINED

The essence of respect for patient autonomy and self-determination is that an appropriately informed adult patient, with adequate decision-making capacity, has the right to refuse any medical therapy, including life-sustaining ones. Not only has a broad ethical consensus emerged to support this principle, but also both statutory law and important judicial decisions in the United States have established this as a legal right of capable adult patients. Under this principle, absent countervailing obligations, the physician should respect a capable and informed patient's decisions to forgo life-sustaining medical care. However, although autonomy gives patients the right to refuse treatment, it does not give them or their surrogates the unqualified right to demand and receive any desired intervention. Rather, patients, or those making decisions on their behalf, are specifically entitled to accept or forgo medical interventions that fall within the standard of medical care.

MEDICAL DECISION MAKING FOR THE PATIENT LACKING CAPACITY

More often than not, patients in the ICU lack sufficient capacity to provide informed consent or refusal of a recommended therapy (Box 102.1). When patients unexpectedly experience acute

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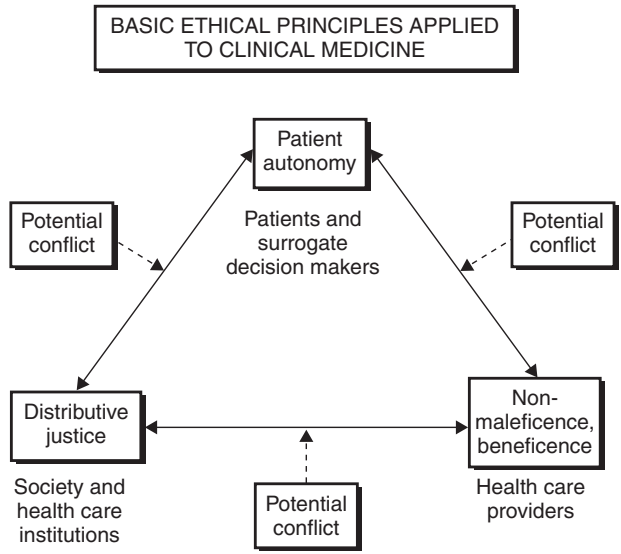


Figure 102.1 Schematic representation of the four basic ethical principles of clinical medicine and their associated moral agents. Double-headed arrows represent potential conflicts and associated ethical dilemmas between two or more principles. *(Courtesy of Paul N. Lanken, MD.)*

BOX 102.1 ■ Criteria Needed for Adequate Decision-Making Capacity

1. Ability to *communicate* a choice
2. Ability to *understand* the information relevant to the decision
3. Ability to *appreciate* the medical situation and likely consequences of various treatment options
4. Ability to *compare* treatment options and *provide* a rational reason for the choice of a specific option

Modified from Appelbaum, PS. Assessment of patients' competence to consent to treatment. N Engl J Med 357:1834-1840, 2007.

life-threatening illness, it is permissible to assume their consent in order to preserve life. However, if patients lack adequate decision-making capacity and are unable to speak for themselves, their right to making decisions passes to a surrogate decision maker or health care proxy to make decisions on their behalf. Ideally this should be someone whom the patient identified as her or his preferred surrogate, such as the holder of a durable power of attorney. Patients often select someone who is close to the patient and who has knowledge of the patient's values, life goals, and preferences about the use of life-sustaining interventions.

Explicit to the surrogate decision-making process is the initial expectation that medical decisions will be made on the basis of what patients would want if they could speak for themselves (called the "substituted judgment" standard). In this regard, an advance directive may be helpful. Unfortunately, a majority of patients have not completed any advance care planning or had any discussions about these issues with those who are close to them.

In the absence of an advance directive (or clear direction from such a document) or knowledge of specific patient preferences, physicians and surrogates should work together to make decisions that are informed by both the patient's physiologic and clinical conditions as well as

the values, goals, and life of the patient. In this process the surrogates provide knowledge of the patient's goals and life values (substituted interest), and the clinicians present information on the risks and benefits of specific interventions and the expectations for recovery from critical illness. Ultimately, in an iterative and collaborative way, a decision based on the "best interests" of the patient is made about a plan of care in which the "pros" of the decision outweigh the "cons."

MEDICAL DECISION MAKING WHEN A SURROGATE CANNOT BE IDENTIFIED

For as many as 5% of patients in the ICU, an appropriate surrogate cannot be found or identified. There are currently no nationally recognized guidelines for managing these situations. Approaches therefore vary by institution, with decision making delegated to the bedside physicians or the institution's chief medical officer, often accompanied by the requirement of a review of the case by the hospital's ethics committee.

Duties of Physicians

The principles of beneficence (being of benefit to the patient) and nonmaleficence (doing no harm to the patient) obligate physicians to promote the health and well-being of the patient and minimize pain and suffering in ways that are caring and respectful of the patient's dignity and worth as a human being. In contrast to these duties, the physician is *not* obligated to provide treatments or interventions that are physiologically ineffective, lacking in medical benefit, or otherwise medically inappropriate. Many ICU clinicians regard as medically inappropriate the use of cardiopulmonary resuscitation (CPR) in response to a cardiopulmonary arrest in the setting of refractory sepsis despite antibiotics and other maximal life-sustaining interventions (e.g., high dose vasopressors).

MEDICAL FUTILITY

The potential conflict between the rights of patients and the obligations of physicians has played out in the long and ongoing debate over the use of futility as a basis for decision making. Some distinguish between physiologic futility and medical futility. If the intervention is determined to be physiologically futile (i.e., it cannot achieve its stated goal), then it can be withheld or withdrawn without the consent or approval of the patient or the surrogate (as it would be medically inappropriate to give a patient a useless intervention).

When invoking medical futility, physicians generally refer to a perceived lack of meaningful recovery (usually based on their own opinion of the patient's apparent low quality of life), a low chance of success, or both. Critics have argued that the term *medical futility* remains ambiguous, too value laden, and too difficult to apply consistently or fairly. Among a slew of ambiguities, it is impossible to exclude the influence of the clinician's personal values, undermining medical futility as ethically sound.

Palliative and End-of-Life Care

OVERVIEW

Most of these deaths in the ICU are preceded by a decision to change goals of care from curative to comfort-only efforts. This makes it an imperative that policies and procedures be in place, based on the core principles and practices of palliative care, to provide high-quality end-of-life care to ICU patients and their families.

Building Trust and Communication Skills

Disagreements at times do arise between health care providers and patients or their surrogates over the goals and plan of care and the continued use of life-sustaining interventions. Although each situation has its own unique features, the majority of these conflicts to some degree involve an absence or loss of trust on the part of the patient/surrogate for the health care team. Therefore, a primary task for the ICU clinician is to establish, nurture, and sustain trust with patients and their family members/loved ones. This trust is ultimately earned by delivering compassionate, high-quality care, and enabled by providing effective communication. Importantly, fostering trust in this way enables the autonomous rights of the patient.

TRUST EARNED BY DELIVERING COMPASSIONATE, HIGH-QUALITY CARE

Clinicians are susceptible to the assumption that by virtue of their position they are entitled to the trust of patients and their families. It is vital to guard against this attitude and instead have the perspective that for each new patient trust must be earned. This trust is fostered by compassionately delivering the best care possible to the patient and then by providing opportunities for the family to learn of the high-quality care that is being provided. These include liberal visiting hours that allow the family to be present for extended periods of time and thus see the full range of care that is being provided; communicating consistently (ideally daily) with the family about the care being provided; and including the family in the patient rounds of the ICU team (see Chapter 106). Lapses in care may occur and can severely undermine the trust that the patient or family has for the health care providers. When medical errors occur, it is essential to regain or maintain the trust of the patient or family by responding in a proactive, transparent, and truthful way (Chapter 107).

TRUST ENABLED BY CONSISTENTLY EFFECTIVE COMMUNICATION

For communication to be effective in the ICU, it must be understandable and welcoming of questions, timely, truthful, respectful and culturally informed. It also entails empathic listening with a genuine desire to know and understand the patient and family.

Communication That Is Understandable and Welcoming of Questions

Medical information provided should be presented in language that is at a level of detail appropriate for the patient or surrogate decision makers to understand. Further, patients and families should be encouraged to ask questions and to express their feelings. The importance of doing these things is emphasized by studies showing that as many as 50% of patients and families are unable to express a clear understanding of basic information about diagnosis, prognosis, and treatment after speaking with physicians. With the increasing diversity of the United States population, health care providers are more likely to encounter patients and families who have limited or a complete lack of proficiency in the English-language. Although the use of family members and friends to provide language interpretation may be all that is readily available on a day-to-day basis, a trained medical interpreter (either in person or by phone) should be employed for critical conversations or discussions about the goals of care.

Frequent and Timely Communication

The importance of frequently updating the families of critically ill patients about their loved one's clinical status and course cannot be overstated. It is recommended that in a very intentional way

the clinicians should meet with the patient's family within 24 to 36 hours to review initial events and issues pertinent to the patient's admission to the ICU. This is not an end-of-life family conference. Instead, as appropriate for each patient, this is a meeting in which hope and determination for achieving recovery are emphasized, whereas perspective is provided on the limits of curative efforts and the benchmarks of recovery or decline are presented. This initial meeting should then be followed ideally by daily efforts to communicate with the family about the patient's clinical course, a task that may be facilitated by including it as an item on a checklist or achieved by having the family present during work rounds. When large or dispersed families are involved, it is usually helpful to identify one individual to serve as the family's spokesperson and the conduit of information between the family and the ICU team.

Truthful Communication

Out of fear of delivering bad news or destroying the hope of the family, ICU physicians may not be completely truthful in discussing the patient's clinical status with the family. In doing this, the physician is actually undermining the principle of autonomy as appropriate decision making requires that the surrogates have accurate and complete information about the patient. Moreover, most families do not consider the withholding of prognostic information as an appropriate way of maintaining their hope. Consequently, the ICU physicians should provide their best assessment of the patient's prognosis while recognizing the uncertainty of such prognostication for individual patients. Not infrequently, however, there will be instances in which patients and families will have strong hopes for an outcome the physician believes is very unlikely to happen. Rather than trying to intellectually convince the family that what they are hoping for is highly unlikely to occur, a more effective approach is to redirect expectations to other, more attainable goals. This might be presented by saying, "I know that you are hoping for … but I don't know if we can make that happen. If not, are there other goals you have for your loved one?"

Respectful and Culturally Informed Communication

Culturally sensitive and respectful dialogue is critical to successfully engaging the diverse populations that ICU clinicians are likely to encounter. Consequently, it is important to be supportive and respectful of the values and views of the patients and surrogates and to assess for specific cultural, ethnic, or religious issues and needs that might impact care or decision making. Significantly, a culturally informed approach to conversations and negotiations may reduce anxiety and the risk of posttraumatic stress disorder in patients and surrogates (see Chapter 105 for guidelines on providing culturally competent care).

Attentive and Empathic Listening

Patients and families are likely to have intense and potentially overwhelming emotional reactions to the ICU experience. These may include, often simultaneously, anger, fear, grief, loss, guilt, frustration, disappointment, and uncertainty. Physicians should attend to these emotions and be attentive to and vigilant for opportunities to express empathic statements. Examples of these types of statements include "I imagine this must be very difficult to talk about," "Tell me more about what you're feeling," "What is most important to you?" or "I'm here to support you."

Family Meetings

OVERVIEW

One of the most important communication tasks in the ICU is the meeting with the patient's family or surrogates, or less commonly, the patient, to discuss a change in the goals of care for

a critically ill and dying patient. A consensus about the goals and plan of care is more likely to occur in the setting of trust and when there has been effective communication with the patient or the surrogates. Regardless of the method employed by the physician to facilitate a decision, preparation is important. Although each patient is unique, there are a number of elements that, if incorporated into the conversation, are likely to increase the chances of a mutually agreeable, patient-focused, goal-directed plan of care. As these types of end-of-life conversations most often occur when the patient lacks decision-making capacity, what is presented next is from the perspective of the family/surrogate decision makers. However, if the patient is able to participate in the discussions, then she or he should be included in the conversations.

MODELS OF MEDICAL DECISION MAKING

Surveys indicate that ICU physicians use one of three models of medical decision making to facilitate a decision about the direction of care. The first is a *paternalistic* approach, in which the physician makes significant choices for patients and family based on the principles of beneficence and nonmaleficence. It is asserted that the physician has the knowledge, expertise, and emotional capacity to process information and make the medically appropriate decision. Although efficient (from the perspective of the health care providers), this approach undermines the patient's autonomy. The second is that of *informed choice,* where the physician provides the medical information but defers to the patient or family for a decision. In contrast to the paternalistic method, informed choice is in accord to the principle of patient autonomy but does not allow physicians to guide medical decision making based on their medical knowledge and experience. Lastly, there is the *shared decision making* model, in which the physician provides information and recommendations and works with the family collaboratively to achieve consensus and come to a mutually agreeable solution.

Of the three, the shared decision making model is recommended as the default approach to end-of-life conversations, although in specific situations the other approaches, in part or in entirety, may be appropriate for a given patient or family.

PREPARATION FOR THE FAMILY MEETING

Spontaneous, chance meetings do occur and can be successful in arriving at a consensus about the plan of care. However, a scheduled meeting, preceded by thoughtful preparation is much more likely to produce a patient-focused outcome. There are three tasks that should be part of the preparation for a meeting to address a change in the goals of care for a critically ill patient. First, it is important to ensure that the family/surrogates know in advance what the meeting is about and that the key individuals will be present for the meeting. This includes individuals who may be the legal decision makers, as well others who could exercise a veto over any decisions made in the meeting. Second, numerous studies have confirmed the value of interdisciplinary care at the end of life. Consequently, the bedside nurse, relevant consultants, and, as appropriate, the patient's primary care provider(s), pastoral care, social worker, and palliative care consultant should be part of the meeting. Finally, in preparing for the family meeting, it is essential that the medical team has a clear understanding of the medical facts and issues and has reached a consensus about the best course of action.

A RECOMMENDED APPROACH FOR FACILITATING THE MEETING TO DISCUSS A CHANGE IN THE GOALS OF CARE

Box 102.E1 presents recommendations for facilitating the conversation about a change in the goals of care. They are not offered dogmatically as the "right way" to conduct an end-of-life

BOX 102.E1 ■ Recommendations for the Family Meeting to Discuss Changes in the Goals and Plan of Care

1. Prior to the meeting, the participants should confer with each other to:
   a. Confirm agreement about the proposed changes in the direction of care.
   b. Review the issues likely to impact the conversation.
2. Immediately before the start of the meeting:
   a. Silence pagers and cell phones. Have sufficient seats for participants.
   b. Have the members of the ICU clinical team, the patient's primary care physician, the patient's specialty care provider (if relevant), social worker or chaplain who knows the patient or family members or both sit throughout the room.
   c. Bring boxes of tissues.
   d. Place a "Family Meeting in Progress" sign on the door.
3. To begin the meeting: The ICU attending physician should:
   a. Summarize the purpose of the meeting.
   b. Ask all of those present to introduce themselves and state their relationship to the patient.
   c. Express appreciation for the family's willingness to participate in the conference.
4. To establish a connection with the family:
   a. Solicit their concerns, fears, and goals.
   b. Ask the family to speak about the life, values, and qualities of the patient.
   c. Clarify the family's understanding of the medical issues.
5. To arrive at a consensus about the plan of care:
   a. Clarify and define terms as appropriate.
   b. Arrive at an agreement with the family about the goals of care.
   c. Present recommended treatment or options, consistent with the goals of care.
   d. Obtain agreement on the plan of care.
6. To conclude the conversation:
   a. Summarize what has been agreed to and the next steps.
   b. Ask for any remaining questions.
   c. Respond to emotional reactions with statements of empathy.
   d. Provide assurances of continued support and attention.
   e. Ask the family to share something special or humorous about their loved one.
   f. If appropriate, invite prayer by the chaplain, family member, or the family's clergy person if present.
   g. Acknowledge the difficulty of the conversation and the decisions that were made.
   h. Note specific strengths of the family.
   i. Again thank the family for their presence.

conversation with a family. These recommendations, however, do summarize what the published literature and expert clinical experience have identified as best practice for facilitating these challenging discussions.

The first element is a premeeting conference among the medical and hospital participants to ensure that there is agreement on the recommendations that will be presented. Once the medical team has assembled with the family, the next step is to establish conditions that provide for an uninterrupted, open, and informed meeting. The conversation then begins with an initial phase where the goal is to establish a connection with the family by eliciting their fears and concerns, discussing the life and values of the patient, and clarifying their understanding of the medical issues. The discussion subsequently moves on to developing a consensus about the goals of care consistent with the life, values, and goals of the patient as well as the physiologic realities of the patient's condition. The meeting concludes with efforts to support and comfort the family.

Managing Conflicts in the ICU

OVERVIEW

Even when the health care providers may be sincere and well meaning in their interactions with patients and families, conflicts with patients, and more commonly their surrogates, do arise in the ICU. Although some of these conflicts involve ethical issues, in most instances these conflicts are related in some way to a loss of trust or a failure to communicate effectively with the patient or family. Thus, the importance of building and sustaining trust and maintaining attention to the competing understandings, perspectives, and expectations of patients and their loved ones is again emphasized as the essential means of preventing or limiting conflict. When a conflict does arise, however, the clinicians should patiently enter into further discussion and negotiation with the patient or the surrogates, keeping in mind those factors that may drive or contribute to the conflict. In most instances, this type of respectful engagement ultimately proves to be successful in resolving the conflict. However, when it does not, there are additional strategies that may facilitate a resolution of the conflict.

FACTORS THAT DRIVE CONFLICT IN THE ICU

Patients, surrogates, and physicians, in addition to their individual personalities, also bring their own sets of beliefs, values, life experiences, and cultural norms to the decision making involved in negotiating the plan of care. It should therefore not come as surprise that parties who are different in so many ways may disagree about the goals of care. Furthermore, patients and families encounter a number of stressors in the ICU that may distort their interactions and communication with the health care providers and thus increase the risk for conflict. These include the confusing, hectic, rapidly changing, and often unpredictable qualities of ICU care, emotions of ambivalence, anger, disappointment, anticipated grief, guilt, and fear; and having to make decisions when the patient's explicit wishes are unknown. An understanding of all these factors should inform the approaches that are used to resolve the conflict.

CONFLICT RESOLUTION: PALLIATIVE CARE SERVICE CONSULTATION

Palliative care specialists have expertise in the recognition and treatment of pain and suffering, communication, conflict resolution, and supportive counseling. Studies analyzing the effectiveness of palliative care consultation in the ICU have demonstrated higher rates of formalization of advance directives and discharge to hospice units, lower use of nonbeneficial life-sustaining interventions, reductions in ICU length of stay and hospital cost, and improved quality of life and bereavement scores by patients and their families. As such, depending on the institution, they may be a helpful resource for facilitating communication, ensuring continuity of care beyond the ICU, and providing emotional support in ways that may enable a consensus to be reached about the plan of care.

CONFLICT RESOLUTION: CLINICAL ETHICS CONSULTATION AND BIOETHICS MEDIATION

Another potential resource for resolving conflict is clinical ethics consultation. Although the majority of discord is not of an ethical nature, ethics consults can be used to clarify ethical ambiguity or provide an additional opinion in a difficult case. In some studies, ethics consults were associated with reductions in many of the same process and outcome measures as observed with palliative care consultations. However, the process of ethics consultation is potentially problematic in that it can produce arbitrary, biased, and at times unilateral decisions and may not meet

the needs of all involved parties. Given these reservations, bioethics mediation has begun to be utilized as a substitute to clinical ethics consultation in some health care settings.

In theory, the handling of disputes via mediation offers a viable alternative by utilizing a shared decision-making model. Mediation is a method of negotiation aimed at achieving a mutually agreeable solution when conflict arises between multiple parties involved in the care of a patient. The intended purpose of mediation is to create a neutral environment where patients and surrogates can be engaged to share their perspective while still providing a forum for physicians to clarify medical facts and express concerns. Although promising, the effectiveness of mediation in the health care setting remains to be determined.

CONFLICT RESOLUTION: TRANSFER OF CARE

On rare occasions, a relationship between the physician and the patient or their surrogates may be irreparably fractured. In this context, it may be appropriate to make a good faith effort to transfer the care of the patient to another clinician. Depending on the situation, this may be done by having another physician at the same institution assume responsibility for the care of the patient or it may involve transferring the patient to another health care facility.

THE HEALTH CARE PROVIDERS AND UNRESOLVED CONFLICT

In most circumstances, agreement can eventually be reached. However, when negotiation and communication fail to resolve the conflict, the ICU team may find themselves in circumstances where they are providing care that they believe is ineffective or harmful to the patient. In these settings, it is important for the medical staff to support each other while continuing in a professional manner to provide the best care possible to the patient.

MEANING AND PURPOSE OF PALLIATIVE CARE

Although some define palliative care as care provided to a person during the final stages of life when disease progresses to the point where the need for symptom management surpasses curative treatment, others, including the World Health Organization (WHO), define it more broadly, as the treatment of symptoms and distress. The latter argue that palliative care should, as a rule, be integrated into curative and restorative care as needed to meet the patient's needs (Figure 102.E1).

Palliative care specialists are dedicated to providing relief from pain and suffering and psychological support to patients and families with substantial burdens from illness. At all times, by both words and actions, the message conveyed by all health care providers must be that, although the ICU team may withhold or withdraw a specific treatment or set of interventions, in no way are they discontinuing or limiting "care." That is, even when cure is unattainable and death is certain, care (e.g., relief of pain and suffering, general hygiene, support of the family, etc.) will still be provided.

SYMPTOM RELIEF

One of the ethical tenets of end-of-life care is that physicians have a moral obligation to ensure a dignified death through the comfort and relief of suffering of a dying patient. It is therefore both ethically and legally acceptable for the relief of suffering to be of high importance during the dying process even if such an intervention includes a risk of hastening death.

Appendix C provides a detailed description of medications commonly used to relieve pain and suffering at the end of life in the ICU. The aim of palliative drug therapy is to keep patients comfortable while they are dying from their diseases. This is sometimes confused with active euthanasia whereby the goal is to intentionally cause the patient's death by the drug's actions. Situations such as these speak to the *doctrine of double effect*. This key principle guiding the practice of end-of-life care holds that in the course of relieving the pain and suffering of a terminally ill patient, if an intervention or treatment has the unintended consequence of hastening the dying process, it is still permissible (as long as the drug is being used for the purpose of symptom relief).

AN APPROACH TO WITHHOLDING OR WITHDRAWING LIFE-SUSTAINING INTERVENTIONS

As a general rule, when the decision has been made to change the goals of care to comfort care only, going forward, the patient should receive only treatments and actions consistent with this goal. Although care should always be tailored to each specific patient, the overall approach that is recommended (Fig. 102.2) is one that anticipates and then prepares for the symptoms the patient might experience, focuses primarily on symptom control both before and after life support is withheld/withdrawn, and remains attentive to the family members and their needs.

In employing this approach three things are emphasized. First, all life-sustaining interventions (including enteral feedings) should be discontinued at the same time rather than in a sequential manner (although the emotional state of the family or cultural issues may make a partial withdrawal more acceptable to the family). Second, all interventions that are not in accord with the revised goals of care should be stopped and restraints and oral/nasal gastric tubes should be removed if not needed for patient comfort. Finally, the ICU team should continue to be engaged both in ensuring the comfort of the patient and in supporting the family.

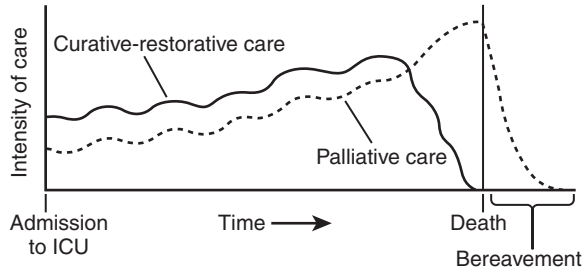


Figure 102.E1 Patient-centered (individualized) model of palliative care provided to a patient and his/her family admitted to an intensive care unit. In this model, palliative care *(dashed line)* is provided concurrently with curative/restorative care *(solid line).* Like the latter, the intensity of palliative care changes to reflect the needs and preferences of the patient and patient's surrogate decision makers and family. Note that palliative care that addresses bereavement needs of the patient's family continues after the patient's death. *(Reproduced with permission from Lanken PN, Terry PB, DeLisser HM, et al: An official American Thoracic Society clinical policy statement: palliative care for patients with respiratory diseases and critical illnesses. Am J Respir Crit Care Med 177:912-927, 2008.)*

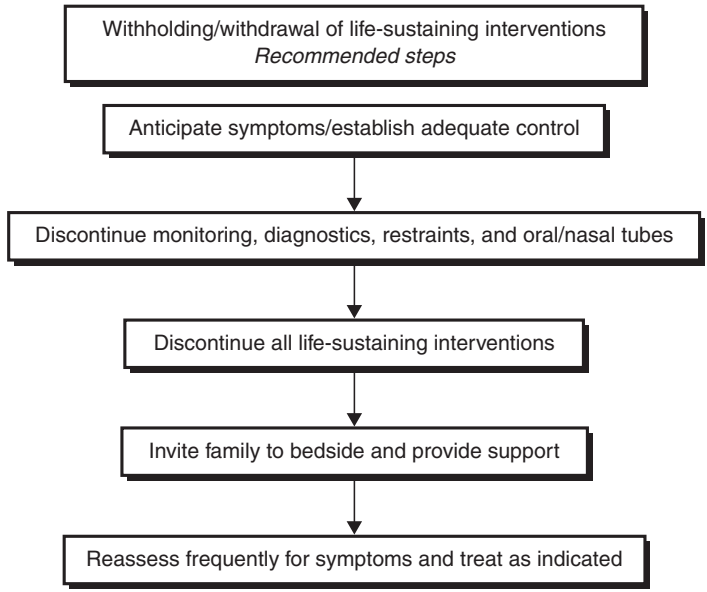


Figure 102.2 Recommended steps for withholding or withdrawing life-sustaining interventions.

EMOTIONAL AND SPIRITUAL SUPPORT OF THE PATIENT AND FAMILY

Effective support of patients and their families goes beyond providing interventions to reduce physical suffering. The withdrawal of life-prolonging interventions or the eventual death of the patient may well be the time of greatest distress for the patient's loved ones. At all times, but especially after life support is withdrawn and after the patient dies, the patient's family and close friends should be provided emotional support by the ICU team and other trained hospital personnel, such as social work or pastoral care. When the family is grieving and the medical staff is struggling with their own emotions of grief, the staff may feel at a loss as to what to say to the family. At that moment, silence is more than adequate and the staff's presence is more than sufficient to provide comfort.

As a means of supporting the patient's loved ones, they should be given ample time to stay in the room with the patient during the dying process and, if they wish, to be present at the time of death as well as after the patient is pronounced dead. Unless there is another critically ill patient waiting for the dying patient's ICU bed, or if the dying process is anticipated to be long, in general the deceased's body should be removed from the ICU after a reasonable time has passed, especially if family members are on their way to the ICU. This permits continuity of medical care and emotional support to be provided by the ICU team who already knows the patient and family well. Furthermore, titration of sedatives and opioids immediately before and after terminal extubation or weaning often requires a high level of nursing care that may be best provided in the ICU.

More information on trust and communication, family meetings, and managing conflict in the ICU, and an annotated bibliography can be found at www.expertconsult.com.

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This longitudinal study of patients with advanced cancer evaluated resource utilization and health care costs at end of life. It reported an association between end-of-life conversations and reductions in the use of life-sustaining therapy, improved perceptions of quality of death, and reductions in health care costs. It also demonstrated no survival difference associated with differences in health care expenditures.

CHAPTER 103

Teamwork and Collaborative Practice in the Intensive Care Unit

Meghan B. Lane-Fall ■ Linda Hoke ■ Cheryl Maguire

What Is Collaborative Practice in the Intensive Care Unit?

Intensive care traces its origins to the mid-20th century, when acutely ill patients such as battlefield soldiers, patients with polio-associated respiratory failure, postsurgical patients, and premature infants were cared for in designated units. One of the factors distinguishing these early intensive care units (ICUs) from other units was the nurse-to-patient ratio. It was recognized very early that sicker patients required greater attention by all members of the ICU care team. Early practitioners of critical care thus appreciated the value of both nurses and physicians in the care of the critically ill patient.

The contemporary practice of intensive care has extended this appreciation of interprofessional practice to embrace other specialized practitioners from a variety of disciplines in caring for the critically ill. Such disciplines are not limited to medicine and nursing, but include a diverse group of practitioners from areas such as pharmacy, respiratory therapy, nutrition, physical therapy, occupational therapy, social work, palliative care, and pastoral care. Health services researchers have demonstrated improved patient outcomes when this multidisciplinary model is employed.

Collaborative practice in the ICU describes a care model in which the strengths of different practitioners are brought to bear to secure optimal outcomes for patients. In this model, patient care and leadership are shared across disciplines. Care protocols promote advancement toward patient care goals without requiring minute-by-minute physician intervention. Patient care rounds, in which clinical information is shared and decisions made, are usually led by physicians, but nurses, pharmacists, and other members of the ICU team are welcome and are active participants in the formulation of a care plan.

What Are the Benefits of Collaborative Practice in the ICU?

Collaborative practice promotes patient safety and optimal outcomes by encouraging shared responsibility for patient care and harnessing the expertise of each discipline involved. When all members of the ICU team (Table 103.1) take an active role in patient care, care goals are achieved faster and more efficiently and both patient and provider satisfaction are improved. The use of ventilator weaning protocols offers an illustration of the benefits of collaborative practice. In settings where a physician order is required to make any ventilator adjustment, ventilator weaning goals are accomplished more slowly than if respiratory therapists are empowered to make changes according to a protocol.

Additional online-only material indicated by icon.

TABLE 103.1 ■ **Intensive Care Unit Multi-disciplinary Team Members***

Team Member	Example of Role
Physician	
Attending physician	Care team leadership and oversight, trainee education
Fellow	Care team leadership, direct care, invasive procedures, trainee education
Housestaff	Direct care, invasive procedures
Consulting physicians	Guide specialized patient care
Primary clinical service	Non-ICU patient care in ICUs that are semi-closed or open in ICU structure
Advanced Practitioner	
Nurse practitioner	Direct care, invasive procedures,† quality improvement initiatives
Physician assistant	Direct care, invasive procedures,† quality improvement initiatives
Clinical nurse specialist (CNS)	Staff education, patient teaching, quality improvement
Nurse (RN)	Direct patient care, administration of medications, patient and family education and advocacy
Pharmacist	Medication oversight, dosing guidance, detection and management of medication toxicity, medication reconciliation, patient and staff teaching, quality improvement
Respiratory therapist	Management of invasive and non-invasive mechanical ventilation, administration of inhaled medications, arterial blood sampling; therapist driven protocols for mechanical ventilation, spontaneous breathing trials and weaning trials; quality improvement
Nutritionist	Selection of nutritional regimen, monitoring of nutritional adequacy, quality improvement
Physical therapist	Direct care, mobilization and ambulation
Pastoral care	Patient and family spiritual and emotional needs
Social worker	Goals of care, family meetings, discharge planning
Patients and families	Shared decision making, participation in daily rounds

*Additional care team members include occupational therapists and palliative care consultants.
†State laws vary on nurse practitioner and physician assistant scope of practice and procedure reimbursement.

Secondly, patient safety and coordination of care improve with collaborative practice. Shared care plans and goals of care for patients serve as protection against adverse events such as medication errors, wrong-sided procedures, and resuscitations that patients or families have declined. Many ICUs use checklists to facilitate the formation and communication of care plans. Checklists have been shown to decrease unnecessary variability in care and promote evidence-based practice. An example of a checklist used during interdisciplinary rounds is shown in Figure 103.1.

An additional benefit to collaborative practice is improved team member satisfaction. The ICU is a high-acuity environment in which practitioners are subject to variable degrees of stress and frustration. Collaborative practice and shared ownership of patient care may diffuse some of the anxiety related to caring for the critically ill, contributing to a healthier work environment.

MICU DAILY INTERDISCIPLINARY PLAN

Date: _____
Housestaff: _____ **On-Call** _____

Previous Shift RN's Concerns
- _____
- _____
- _____
- _____
- _____
- _____

Changes since initial assessment
CV/hemodynamics _____
- _____

Pulm _____
- _____

Neuro _____
- _____

GI/GU _____

Sedation/Pain ❑ N/A
RASS: _____ CAM/ICU _____
Sedation: _____ Decreased? Y__N__
Why? _____ Why not? _____

Pain? _____ Anxiety? _____

Prophylaxis
- DVT- Heparin ____ Compression _____
- HOB > 30 ____ no, Why? _____
- Orthotics? _____
- GI prophylaxis? _____
- PT consult needed? _____

Nutrition/Endocrine
TPN _____ (yes, why? _____)
TEN @ goal? (No, why? _____)
Glucose > 150 ____ need gtt? _____
Bowel regimen? _____

CODE STATUS: DNAR ____ FULL _____
RN _____ Initial ____ Shift ____
RN _____ Initial ____ Shift ____

❑ Plan reviewed by Fellow/Attending:
Signature: _____

IV Access
TYPE _____
Insertion date: ___ /___ /_____
Sites ok:
Site documented on IV catheter record? ___
Adequate access? _____
Can any be removed? _____

Restraints
❑ MD Order ❑ N/A
❑ Form filled out

Indication for foley: ❑ N/A
❑ Unstable (hemodynamic or severe hypoxia)
❑ Uncleared spine (female only)
❑ Obtunded
❑ Urologic requirement (surgical issue)
❑ Wound contamination

Family Discussion/Issues
- _____
- _____

Skin/Wounds
- _____
- _____

Problem/Plan (Document progress on back)
❑ _____
❑ _____
❑ _____
❑ _____
❑ _____
❑ _____
❑ _____
❑ _____
❑ _____
❑ _____
❑ _____
❑ _____
❑ _____

Figure 103.1 Example of a Care Plan Checklist to Be Used during Multidisciplinary Daily Rounds in an Intensive Care Unit. CAM/ICU, Confusion Assessment Method for the Intensive Care Unit; DNAR, do not attempt resuscitation; DVT, deep venous thrombosis prophylaxis; Fellow/Attending, fellow/attending physician; GI, gastrointestinal; gtt, continuous intravenous infusion; GU, genitourinary; HOB, head of bed; IV, intravenous; MD, physician; ok, okay; PT, physical therapy; RASS, Richmond Agitation-Sedation Scale; RN, registered nurse; TEN, total enteral nutrition; TPN, total parenteral nutrition; Y/N/N/A, yes/no/not applicable. *(Courtesy of Barry Fuchs, MD, and Cheryl Maguire, RN.)*

What Are the Challenges of Collaborative Practice in the ICU?

Collaborative practice as a model is distinct from other care paradigms that are predicated on the philosophy that the physician is not only the team leader, but the sole authoritative decision maker about patient care issues and other ICU administrative matters. Indeed, inherent within the concept of collaborative practice is that each member of the ICU team is valued for his or her unique training and professional perspective and can contribute to the care of the patient. Successful collaborative practice requires commitment from all team members and explicit expectations from leadership about ICU teamwork. Collaboration is also enhanced by a "culture of safety," in which all team members are encouraged to voice their concerns about patient care irrespective of the discipline or level of training to which they belong.

Despite the demonstrated benefits of collaborative practice, there are a number of challenges to effectively implement a model of patient care reliant on teamwork. These difficulties include hierarchical leadership structures, time pressures, and limited resources.

A hierarchical leadership structure, while deeply ingrained in many institutions, may hinder collaboration by preventing effective communication across disciplines and between junior and senior team members. Incorporating physicians, nurses, and other care team members into leadership roles demonstrates a commitment to collaboration and facilitates quality and performance improvement initiatives. One approach to flattening hierarchical leadership, the Unit-Based Clinical Leadership model, is presented in Figure 103.E1.

Time is another important consideration in developing collaborative practice. Developing multidisciplinary protocols often involves education and information sharing between colleagues with different professional backgrounds before consensus about clinical care protocols can be reached. Partnership in clinical care and leadership requires coordination of sometimes disparate schedules.

Finally, personnel resources may limit the extent to which teams are able to function effectively. Specifically, clinical nurse specialists, pharmacists, nutritionists, physical therapists, and pastoral care professionals may have high clinical workloads that limit their ability to participate in patient care rounds, when clinical plans are often formulated.

Simulation in the Promotion of Teamwork and Collaborative Practice

Simulation is increasingly recognized as a valuable tool in promoting effective teamwork in high-acuity environments. ICU teams can participate in these simulations together, troubleshooting communication or role assignment without concern for patient harm. It can be especially enlightening for team members to swap roles. For instance, when a physician assumes the role of a nurse in a simulation, the physician may develop a better understanding of the challenges faced by nurses when executing tasks such as patient monitoring or medication administration during critical situations.

Simulation also offers the opportunity to train team members in techniques proven to improve communication in high-stakes environments. Lessons learned from the aviation industry about teamwork in critical situations include the importance of crew resource management, situational awareness, and explicit task distribution.

Either high-fidelity (realistic scenarios with interactive manikins) or low-fidelity (less realistic) simulators may be used. Irrespective of the details of the simulation exercise, it is important that team members work together in scenarios similar to those faced in actual patient care. After the simulation is complete, adequate debriefing time is crucial to cement learnings from the exercise.

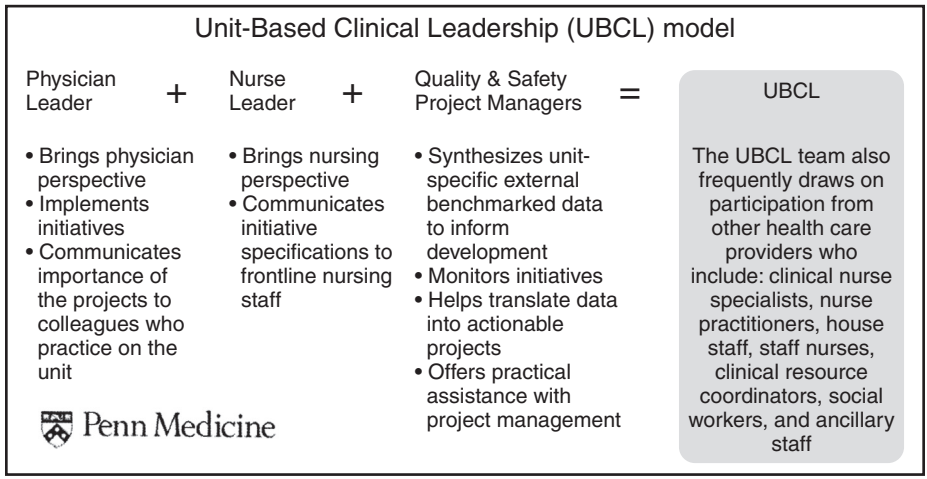


Figure 103.E1 Case study in collaborative leadership: Unit-Based Clinical Leadership. The University of Pennsylvania Health System has transformed the way the global clinical quality strategy is translated to the local patient care environment by instituting a local leadership model called the Unit-Based Clinical Leadership (UBCL). The model is a leadership approach characterized by egalitarian partnership in which nurses, physicians, and allied health professionals share accountability for quality and patient safety outcomes. UBCLs were designed to establish and nurture partnerships to transform clinically relevant and patient- and family-centered issues into systemic, sustainable changes. Team members are mutually accountable for strategic outcomes and facilitating goal achievement. Rather than prescribing protocols and processes that dictate how each unit should accomplish system-wide clinical quality goals, hospital leadership defers decision-making to UBCL teams. The UBCL teams are tasked with monitoring and improving patient safety, clinical performance, patient- and family-centered care, and transitions across the care continuum.

Each patient care unit has its own UBCL. The UBCL teams consist of three core members: a physician leader, a nurse leader, and a quality/safety project manager. The unit leadership teams meet weekly to review metrics, troubleshoot problems, and develop plans for short- and long-term projects. The leaders support interdisciplinary rounding, in which nurses and physicians meet daily with patients and families, social workers, pharmacists, and other team members to make decisions about the plan of care. The UBCL teams analyze trends in quality data, monitor progress toward quality goals, and identify potential areas for improvement. Should a UBCL team identify an opportunity for improvement, the nurse manager, as liaison between the UBCL team and clinical nurses, will seek input from front-line clinical nurses to gain a deeper understanding of the problem as well as to develop and implement effective solutions.

This unit-focused leadership model has enhanced effectiveness and efficiency across the organization and has enabled rapid-cycle change in quality improvement initiatives. The UBCL model has been at the forefront of collaborative practice by advancing the unit leadership model and bringing together the collective expertise of nurses, physicians, and quality coordinators in the oversight of care delivery and operational processes. *(Figure used with permission. © 2009, The Trustees of the University of Pennsylvania.)*

Conclusions

The complexity of modern critical care requires teamwork and effective interprofessional collaboration. Significant time and resources are needed to support collaborative practice, but the demonstrated improvements in patient safety and quality of care suggest that these resources are well spent. Checklists, shared leadership, and simulation are all tools that may facilitate successful collaborative practice in the ICU.

An annotated bibliography can be found at www.expertconsult.com.

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Rose L: Interprofessional collaboration in the ICU: how to define? Nurs Crit Care 16:5-10, 2011.

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This is an academic intensive care unit's description of one approach to conducting multidisciplinary conferences discussing patient complications. This model is offered as an alternative to the physician-only morbidity and mortality conference.

Thompson DR, Hamilton DK, Cadenhead CD, et al: Guidelines for intensive care unit design. Crit Care Med 40:1586-1600, 2012.

A multidisciplinary group of authors including clinicians and architects offered guidance on the optimal physical design of the intensive care unit. Design suggestions incorporated the need for multidisciplinary team meeting space and the ability of patient rooms and hallways to accommodate large groups on patient care rounds.

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This article explored economic considerations in the modern provision of critical care. It discussed cost considerations in forming a multidisciplinary care team, raising questions about balancing personnel cost with efficiencies in patient care.

CHAPTER 104

Family-Centered Care and Communication with Families of Intensive Care Unit Patients

Mark E. Mikkelsen ■ Robin Hermann ■ Horace M. DeLisser

Approximately 20% of patients in the United States will die in an intensive care unit (ICU) with the majority of these deaths involving the withholding or withdrawal of life-sustaining therapy. High-quality patient-centered critical care depends on effective communication that elicits the patient's values and preferences for care. Because many critically ill patients during their ICU stay lack the capacity to make informed decisions about their care, critical care practitioners more often than not are dependent on families (and others who have been close to the patient and equivalent to family members) to obtain information on the goals, values, and preferences for the patient's care.

Unfortunately, despite the importance of families to shared decision-making in the ICU, family members of critically ill patients often do not understand the diagnoses, prognosis, or plan of ICU care for their family member. For this reason it is not surprising that family members welcome interactions with the ICU provider team that enable them to both obtain this information as well as consistently communicate with those who are caring for their family member. *Family-centered rounds* represent an emerging approach for meeting this need. The strategies for facilitating family-provider communication may initially appear challenging to the health care providers. However, families value the clinicians' communication skills as much as (and maybe more at times than) their clinical competence.

Family-centered rounds are a component of the broader concept of family-centered care, the key elements of which are an authentic partnership between the health care providers and the patient/family based on mutual respect, trust, open communication and information sharing, collaboration, and shared decision-making. Developed initially in the context of care for chronically ill pediatric patients, family-centered care has now been widely endorsed as a core competency for health care providers by numerous health care organizations and institutions including the Institute of Medicine, professional nursing and physician societies, and accrediting agencies for health care organizations and graduate medical education. Other resources and skills to provide family-centered care include palliative and end-of-life care (see Chapter 102), teamwork and ICU organization focused on patient and family care (see Chapter 103), cultural competency (see Chapter 105), and family-friendly practices such as liberal visitation policies.

Having the family join daily work rounds provides a structure and process that can enhance effective communication between health care providers and the patient and the patient's family. This approach has a number of important potential benefits (Box 104.1) that contribute to the goal of promoting high-quality, patient-centered, and family-centered care as well as minimizing the long-term neuropsychological distress incurred by family members of critically ill patients.

BOX 104.1 ■ Objectives of Having the Family Join Daily ICU Work Rounds

- Demonstrate respect and foster trust.
- Affirm and support the family.
- Enable timely opportunities to learn of the concerns and fears of the family.
- Establish a pattern of patient-focused, goal-directed conversation based on the patient's values, preferences, and life story.
- Ensure the family has accurate and current information about the patient.
- Provide a consistent message to the family.
- Facilitate timely and appropriate end-of-life conversations.

An Overview of Family-Centered Rounds

Family-centered rounds, initially introduced into pediatric care in the early 2000s, are now increasingly more common in adult critical care medicine. However, the proportion of adult ICUs in the United States to have adopted this approach is unknown. Likewise, relatively few studies have examined the effects of family-centered rounds on patient outcomes or family satisfaction, with most of the data being drawn from the pediatric experience. Consequently, it is important to exercise caution when extrapolating the published data to the practice of adult critical care, particularly in light of the fact that ICU mortality is substantially lower in pediatric populations. Despite these limitations, one can conclude that the family's participation in rounds often provides new and relevant information about the patient without significantly lengthening the duration of rounds, improves communication between clinicians and family members, and is associated with higher levels of family and staff satisfaction. Further, the data suggest that family members, when appropriately coached, are able to accept and adjust to the expectations and culture of multidisciplinary ICU rounds. A number of elements have been reported to enhance the quality of the family's experience while participating in rounds, and these have been incorporated into the recommendations in Box 104.2.

Potential limitations that have been voiced about family-centered rounds fall principally into two categories. First, families may be intimidated by the health care providers, uncomfortable discussing their family member in "public," or just too overwhelmed by the situation to meaningfully participate in rounds. Thus, the benefit to the family might be quite limited. On the other hand, there has been concern that the presence of families may disrupt the process of rounds in ways that stifle honest, open discussion by members of the medical team, increase the duration of rounds, or reduce the amount of teaching. Attention to these concerns is reflected in the approaches outlined in the following discussion.

A Recommended Approach for Conducting Family-Centered Rounds

One suggested approach for conducting family-centered rounds includes actions taken before and after rounding on the patient (see Box 104.2). This is not to assert that this is the only way to conduct family-centered rounds. Certainly, ICU clinical team members are encouraged to adapt these recommendations to their clinical area and practice style. Further, each family is different, and thus clinicians have to be prepared to adjust their approach to the challenges and the potential uniqueness of each situation and each family.

BOX 104.2 ■ Recommendations for Conducting Family-Centered Rounds

Before Rounds (Preparing the Family to Participate in Rounds)

- On admission, inform the families of patients about the daily multidisciplinary rounds and invite them to participate.
- Provide the family with written information on the process of rounds and their role in participating in it.

During Rounds

- Each day, before beginning, invite family members who are present to join rounds.
- Form a circle that includes the family if rounding outside of the room and a semicircle if rounding inside the room.
- If this is the first time the family is participating in rounds, do the following:
  - Describe the structure of rounds: presentation of medical data, followed by a formulation of the assessment and plan. Then inform the family that at the conclusion of the assessment and plan, the facts will be summarized for them, followed by an opportunity for the family to ask questions or make comments.
  - Introduce the members of the medical team; subsequently, introduce new individuals as they join the team.
- Intentionally solicit needed information from the family.
- Closely observe and listen to the family to better understand the life and preferences of the patient, as well as the factors that may influence the family's ability to speak on behalf of the patient.
- Manage unsolicited comments or questions in a way that preserves the efficiency and productivity of the rounds.
- If there are questions that require more time than available during rounds, their importance should be acknowledged and arrangements made to address them after rounds.

After Rounds

- Have a member of the medical team routinely follow up with the family to address additional questions or to review of the plan of care.

BEFORE ROUNDS: PREPARING THE FAMILY TO PARTICIPATE IN ROUNDS

On admission, the physicians and nurses should inform family members that multidisciplinary, family-centered rounds occur daily and that they are invited to attend. The verbal information should be paired with a written document (written at a sixth-grade reading level if possible) that is given to the family, which describes the rounding process and the expectations for the family's participation in the rounds.

DURING ROUNDS

Each day as the ICU team assembles at the patient's room, before the discussions of the patient have started, the family should be invited to join rounds. The goal is to have the family feel like welcome members of the team, not intruders. It is recommended that the ICU team initially review the medical data and formulate the assessment and plan, using language that is understandable to family and soliciting from them information (medical or otherwise) about the patient as needed. During the medical presentation, the family may interject unsolicited comments or ask questions. These interruptions may be very timely and helpful, and thus they should not be discouraged; instead they should be managed in a way that preserves the efficiency and productivity

of the rounds. One way of doing this is to encourage the family to save their questions and comments to the end of rounds. Once the medical and nursing discussion has been completed, the significant clinical issues and plan of care should be succinctly and clearly summarized for the family. This is followed by an opportunity for the family to offer comments or ask one or two questions. If the family has questions that require more time than allowed during rounds, the importance of their questions should be acknowledged. Furthermore, arrangements should be made for someone from the ICU team to return after rounds at a specified time to answer the family's questions. When the family is participating in rounds for the first time, a few moments should be taken at the start to describe the process for them as well as to introduce the members of the ICU team. One should also remember to introduce new members as they subsequently join the ICU clinical team.

FOLLOWING ROUNDS

It is useful after the completion of rounds to routinely have a member of the ICU clinical team (e.g., bedside nurse or house officer) follow up with the family to determine if they have any additional questions and to review the plan of care.

Issues Related to Family-Centered Rounds

INEXPERIENCED PROVIDERS

Family-centered rounds can be a unique challenge to inexperienced providers. The added dynamic of incorporating families into rounds for someone who is also learning to care for critically ill patients (e.g., housestaff) or learning to lead the team (e.g., junior faculty) can be daunting. This speaks to the need on an institutional level for formal education (e.g., didactics, written handouts, simulation exercises) and ongoing feedback (e.g., mentored observation) to ensure that the provider is prepared for and competent to conduct these rounds. The ability to facilitate family-centered rounds can be further enhanced by providing opportunities for clinicians at all levels inexperienced in this type of rounding to carefully observe experienced physicians who can model professional, compassionate, and effective communication skills with family members. Further, there is value in intentionally reflecting on and learning from those inevitable situations in which the family's presence on rounds proves difficult and challenging. Ultimately, just as with any other technique in medicine, one needs to complete a sufficient number in order to become both comfortable with and proficient at the procedure. As noted, ICU clinicians will need to develop an approach with which they are comfortable, yet be prepared to adapt their approach to different families as needed.

RESPONDING TO THE DISRUPTIVE FAMILY

Although the family's participation in rounds should be valued because of its potential to enhance communication and shared decision making, providing the best care possible to the patient is still paramount. Consequently, if the family's presence on rounds becomes disruptive or detrimental to the care of the patient, initial efforts should focus on clarifying expectations and setting limits. The participation of families in rounds is ultimately a privilege that can be revoked. Thus, if these initial efforts prove unsuccessful, then alternative arrangements should be made to meet the needs of the family and to engage them outside of rounds. Hopefully these situations are uncommon and the alternative arrangements are often needed only for a brief period of time. It is essential that the response to the disruptive family be developed in a collaborative way by the ICU team, including physicians, bedside nurse, unit nurse and medical

managers, social worker, chaplain, and respiratory therapists, if appropriate. This should ensure that all team members are agreeable to and comfortable with the plan of action and thus can fully support and carry it out.

ADDRESSING GOALS OF CARE AND END-OF-LIFE DISCUSSIONS DURING ROUNDS

It is generally recommended that meetings to discuss transitions of care from curative efforts to comfort-only care be planned events, as certain preparations enhance the quality of the conversation with the family (Chapter 105). However, because of the significant morbidity and mortality of critically ill adult patients, spontaneous and unplanned discussions regarding goals of care and end of life can and do occur during daily rounds. These conversations may be triggered by some aspect of the patient's condition that presents a "teachable" moment for the medical team to engage the family or provide clarity to the family about the gravity of their family member's condition. These situations call for sensitive and empathic communication that accurately describe the patient's condition. In doing this, it is important to acknowledge the stress of having a critically ill family member and the fear that the family member will die. Another related challenge to acknowledge is the burden of being asked to state the patient's care preferences when an advanced directive is not available and when there have been little or no discussions between the patient and the family about end-of-life issues. In this regard there is evidence that some families may feel rushed to make a critical decision during family-centered rounds. Thus, although the conditions may be right for a specific conversation and definitive decision on rounds about a change in the direction of care, it may be more appropriate and effective to use these impromptu conversations on rounds about the direction of care as a bridge to a further, more formal discussion outside of rounds in a more private location (see Chapter 103).

ACKNOWLEDGING UNCERTAINTY, ERRORS, AND OMISSIONS

Uncertainty is an undeniable feature of the practice of critical care medicine, as are errors and omissions in the care provided. Published data indicate that families accept that prognostic uncertainty is an unavoidable reality of medicine. Therefore, the clinicians should not be fearful of acknowledging the uncertainty of care, while highlighting the efforts that are directed at obtaining answers to better treat the patient. To facilitate trust, one should be as open and transparent as possible. However, one should also consider limiting "who communicates what" with a family that has taken to asking a variety of ICU team members about the family member's prognosis and getting mixed or conflicting messages in response. Likewise, lapses in care should be presented (with appropriate context and explanation) during rounds and not edited out of the discussion. However, there may be infrequent situations where it is appropriate to discuss selected issues outside of rounds if it is the judgment of the clinical team that it would be in the patient's best interest to do so.

INCORPORATING TEACHING INTO ROUNDS IN THE PRESENCE OF FAMILY MEMBERS

A concern about family-centered rounds in teaching hospitals is that the quality and amount of bedside teaching of trainees may be diminished by the presence of the family. This is based on fears that the time and attention that could be used for teaching is given to the family and the attending physician may be less comfortable "teaching" when the family is present. In anticipating these concerns, the attending physician can address them in a number of ways. First, the family should be informed that teaching is an important part of rounds. Second, the attending

physician should appreciate the risk to trainee education and thus be intentional about teaching, either coming prepared to present something at the start of rounds or devoting time at the end if the opportunity does not arise during the rounds. Lastly, the attending physician should periodically query the team about whether an adequate amount of time is being spent on teaching during rounds. In addition, the opportunity to improve one's communication skills through this approach to patient care should be acknowledged as essential to the development and maturation of a clinician in training.

An annotated bibliography can be found at www.expertconsult.com.

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This is an excellent review of the experience of surrogate decision makers in the ICU, providing a summary of the skills required for effective and empathic physician-family communication.

Schiller WR, Anderson BF: Family as a member of the trauma rounds: a strategy for maximized communication. J Trauma Nurs 10:93-99, 2003.

This paper detailed the implementation of family-centered rounds in a trauma ICU. The authors reported that despite initial misgivings by some team members, the presence of family members on rounds was subsequently evaluated favorably by participating families and nurses.

CHAPTER 105

Providing Culturally Competent Care

Horace M. DeLisser

Patients in the intensive care unit (ICU) are not only medically complex, but also diverse in terms of culture, race, ethnicity, religious and spiritual expression, English-language proficiency, sexual identity and orientation, and beliefs about illness and health. Differences in culture between the physician and the patient (or the patient's family) are often the basis for distrust, misunderstanding, and miscommunication that lead to dissatisfaction and anger for the patient and family or frustration and impatience for the physician. As a result, patient care may be compromised or conflicts may arise between the ICU team of caregivers and the patient and family. Failure to account for the impact of cultural differences at the patient-provider interface is also likely a factor in some of the racial and ethnic health disparities in the United States (Figure 105.1).

A Conceptual Framework for Cultural Competency

Although cultural competency involves issues of race and ethnicity, it also includes issues of socioeconomic status, gender, age, sexual orientation, and spirituality and religion. In addition, cultures need to be understood as both dynamic and heterogeneous and distinguished from inaccurate stereotyping of individuals of a certain category of diversity. Further, there is also recognition that medicine (and health care in general) has its own culture. In the context of the physician-patient/family relationship, cultural competency therefore refers to the ability to bridge differences in culture between the physician and the patient or family so as to provide respectful, compassionate, and effective care. Framed in this way, cultural competency is an issue of professionalism and is a key skill in the repertoire of a physician providing state-of-the-art ICU care. For physicians, cultural competency is conceptualized as involving three components: (1) self-awareness, (2) development and refinement of cross-cultural communication, and (3) negotiation skills and knowledge of cultural norms and health-related disparities. Importantly, the acquisition of cultural competence by physicians and other members of the ICU team is an ongoing process that requires both sensitivity and humility.

CULTURAL COMPETENCY: ONGOING SELF-AWARENESS

Cultural competence first involves an ongoing and emerging recognition of one's own cultural influences (including the culture of medicine) as well as personal biases and prejudices. In particular, this process of self-awareness includes an appreciation of those culturally based factors that trigger discomfort, fear, anxiety, or anger (e.g., "buttons" that can be "pushed" to which one is emotionally reactive). In considering these kinds of issues, the initial reaction is often to deny the possibility or presence of any personal bias. Consequently, the self-acknowledgment of these issues requires insight, humility, and strength. Importantly, their presence does not mean that one is an inherently "evil" or a "bad" person. In the end, self-awareness develops as a result of purposeful and intentional effort. An individual can promote self-awareness on an ongoing basis by the following activities: narrative writing and journaling of clinical and professional experiences as a means of reflection, exposure to a variety of culturally informing

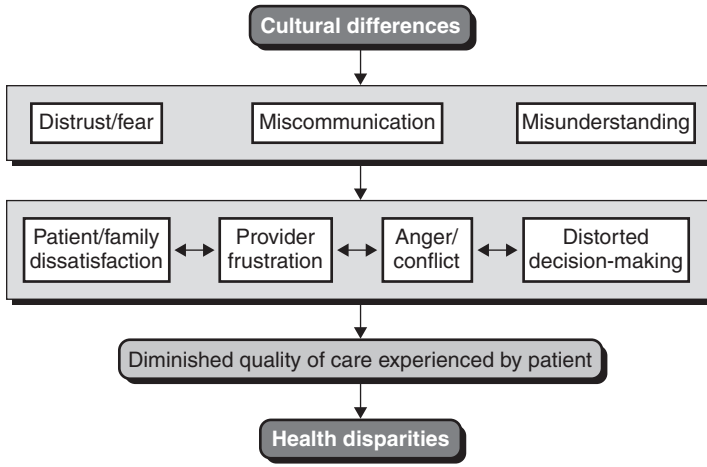


Figure 105.1 The potential impact of cultural differences between providers and patients/families.

literature and media, and deliberately seeking out colleagues with whom one can speak safely about these issues.

CULTURAL COMPETENCY: ONGOING DEVELOPMENT AND REFINEMENT OF CROSS-CULTURAL COMMUNICATIONS AND NEGOTIATION SKILLS

At least three communication skills are particularly pertinent to cultural competency: eliciting and understanding the patient's or family's understanding of the meaning and significance of the patient's illness, effectively using interpreters, and appropriately engaging culturally insensitive colleagues.

Eliciting the Explanatory Model

Patients and their loved ones bring to their ICU experiences beliefs about the causes, meanings, and significance of the patient's illness, as well as expectations about the course of treatment. These beliefs, described collectively as the explanatory model, are shaped to varying degrees by their cultural backgrounds and experiences. Knowing and understanding the explanatory model of the patient/family enable more effective communication on a day-to-day basis and can facilitate discussion and negotiation around goals of care and end of life. A number of communication strategies and mnemonics have been described for eliciting the explanatory model (Table 105.1). They all, however, emphasize the importance and value of (1) respectful, attentive, nonjudgmental listening; (2) listening with genuine curiosity; (3) humility; (4) open-mindedness; (5) empathy; (6) patience; and (7) an attitude of negotiation and collaboration. This information may be obtained in a formal interview or meeting. More often than not, however, it will be acquired over several encounters, with the physician being alert for opportunities during conversations with the patient/family in which open-ended questions can be asked that enable the medical professional to capture their beliefs and expectations.

Use of Language Interpreters

There is an abundance of evidence pointing to the potential for error, editing, filtering, and distortion when family or friends are used to provide interpretation services. Thus, although there are situations in which it is unavoidable, the use of untrained family members or friends to provide

TABLE 105.1 ■ **Mnemonics for Cross-Cultural Communication**

Mnemonic	Reference
LEARN Listen, Explain, Acknowledge, Recommend, Negotiate	Berlin EA, Fowkes WC: A teaching framework for cross-cultural health care: application in family practice. West J Med 139:934-938, 1983.
ETHNIC(S) Explanation, Treatment, Healers, Negotiate, Intervention, Collaborate, Spirituality/Seniors	Kobylarz FA, Heath JM, Like RC: The ETHNIC(S) mnemonic: a clinical tool for ethnogeriatric education. J Am Geriatr Soc 50:1582-1589, 2002.
ESFT Explanatory model of health and Illness Social and environmental factors Fears and concerns Therapeutic contracting	Betancourt JR, Carrillo JE, Green AR: Hypertension in multicultural and minority populations: linking communication to compliance. Curr Hypertens Rep 1:482-488, 1999.
RESTORE Respect the journey or the experiences of your patient Engage your patient—listen with the intent to be influenced Sensitivity to the patient's perspective Teach the patient your perspective Open-mindedness Reach common ground Exercise humility	Carter-Pokras O, Acosta DA, Lie D, et al. for the National Consortium for Multicultural Education for Health Professionals: Curricular products from the National Consortium for Multicultural Education for Health Professionals. MDNG: Focus on Multicultural Healthcare 2009. Accessible at https://depts.washington.edu/omca/dev/cc_prime/tools/RESTORE_mnemonic.html. Accessed June 26, 2012.

language interpretation is far from ideal and is to be discouraged. Instead a trained individual, either in person or via a telephone or online service, should be solicited to provide the medical interpretative services. Admittedly in a fast-paced ICU in which the patient's condition may be changing rapidly, the use of telephone or live interpretation may not be practical in all situations. But certainly a trained interpreter should be used for critical updates of the patient and for goals of care and end-of-life conversations.

Engaging Colleagues around Issues of Cultural Insensitivity

It can be challenging to respond to peers and colleagues who make remarks or demonstrate behaviors that appear to be culturally insensitive. However, as professionals there is a need for physicians to "police" themselves, seeking always to raise the expectations for professional conduct. Certainly the timing, location, and the way the conversation is initiated will have to be individualized for the specific situation. A successful approach, however, is likely to be one that (1) assumes goodwill on the part of the colleague, (2) is not judgmental or accusatory, and (3) focuses on the specific offending words or behaviors and the reactions they caused. Although not everyone will react well, the conversation that is initiated may provide insights to a colleague who may not be aware of the inappropriateness of his or her words or actions.

CULTURAL COMPETENCY: ONGOING ACQUISITION OF KNOWLEDGE OF CULTURAL NORMS AND HEALTH-RELATED DISPARITIES

The first goal is to become knowledgeable about the cultural beliefs, values, experiences, and history of the populations that one regularly treats. A host of content and curricula, national

conferences, and case-based resources can be found online and should be sought out. However, in a number of ways, choosing to ask and learn from patients and their families is the best place to start when seeking this kind of cultural information. In addition, as is done in other clinical aspects of medicine, an approach whereby interesting, challenging, or frustrating cases are used as prompts to learn more is encouraged.

In considering information pertinent to a specific cultural group, it is vital to distinguish between stereotyping (the false and dangerous assumption that everyone in a given culture is the same) and valid generalizations (awareness of cultural norms). Generalizations provide a starting point and a basis for an initial understanding, but in no way do they exclude consideration of individual characteristics such as acculturation, education, nationality, and personal beliefs. Thus, while knowledge of group norms is helpful, it is more important to develop the cross-cultural communication skills that enable you to engage each patient as an individual, with a unique social and cultural experience. So, for example, rather than merely learning that African Americans may be mistrustful of physicians, which may or may not be true for a specific patient or family, it is helpful to also develop the ability to recognize the signs of mistrust as well as the skills for establishing, nurturing, and sustaining trust (discussed later).

Issues of Culture in the ICU

There are numerous challenges to providing culturally sensitive, appropriate, and informed care to critically ill patients. Some of these include navigating situations where there is racial or ethnic distrust, accounting for the impact of cultural issues on end-of-life decisions, and respectfully engaging the spirituality of patients and families.

OVERCOMING RACIAL OR ETHNIC DISTRUST

Patients from minority, disadvantaged, or marginalized groups *may* bring with them distrust or suspicion of physicians, and the health care system in general, based on personal experiences of real or perceived bias or mistreatment. These emotions may be reinforced by wider societal phenomena or historical events that contribute to a collective group distrust and suspicion of medicine. This is particularly the case with respect to the well-documented abuses that occurred in the U.S. Public Health Service (USPHS) Syphilis Study at Tuskegee, which have had a lasting impact on the collective psyche of a large number of African Americans. It has led to an undercurrent of suspicion of medicine in general and biomedical research in particular.

Respect, patience, truthfulness, honesty, and a genuine effort to listen and respond to the concerns of patients and families will go a long way toward ensuring a positive outcome when issues of race or ethnicity may be part of the dynamic. Further, it is important to avoid responding with anger or defensiveness if the motivations of the physicians or institution are questioned, emphasizing instead that the patient will receive the best possible care. In the end, the most effective way to overcome racially and ethnically based distrust or suspicion is to earn trust by working diligently, patiently, and compassionately to provide high quality care to the patient.

INCORPORATING CULTURE IN END-OF-LIFE DECISION MAKING

Although American and Western cultures focus on the individual and the protection of personal autonomy, for many other cultures the family or the wider community are paramount. This in turn may influence the way patients and their families make decisions or resolve conflicts. Nursing, pastoral care, and social work staff may be particularly helpful in gauging this aspect of the family dynamic and in helping the family understand that decisions should be based on what the patient (not the family) would likely desire, based on his or her stated wishes, relevant experiences, and personal values.

It is important to recognize that while conversations about changing the focus of care at the end of life to comfort measures may be seen by advantaged or more financially secure patients as positive efforts to respect autonomy, poor or disadvantaged individuals may instead view these discussions as an attempt to deny them essential treatments. Further, for a patient without a strong support network of family and friends and for whom "home" does not really exist, such as a chronically homeless individual, the opportunity to die outside of the hospital ("at home among family and friends") would not carry much appeal.

Patients will often use their spiritual beliefs to inform their medical decisions. However, although we place value on respecting the religious beliefs and expression of patients, when significant medical decisions are involved, particularly when there are potentially life-threatening consequences, the physician has an obligation to try to ensure that religion-based decisions are derived from authentic, settled, noncoerced beliefs that are internally consistent. Ultimately, this involves a respectful conversation focused on exploring these issues, which may start with the physician but may be continued or completed with the patient's family, a pastoral care provider, or the patient's own spiritual advisors.

It is also important to appreciate that a patient's personal values may differ significantly from the values corresponding to his or her stated religion. For example, invoking a specific religious theology is relevant only if that tradition is still meaningful to the patient. Moreover, it is not uncommon for an individual to be confused or ignorant about the beliefs of their religious faith, leading to misstatements or misrepresentation of those beliefs. To confirm the accuracy of religious assertions, it may be helpful to involve pastoral care staff or to suggest that the family discuss relevant issues with clergy from their faith.

Much importance is placed on the "biologic" family of the patient, with the reflexive tendency of seeking their involvement and input. However, it is important to understand that for gays and lesbians, the patient's relationship with his or her biologic family may be complex and evolving. The family may not know the patient's sexual orientation and the patient may have chosen not to reveal it to them; the relationship between the family and the patient may have become strained after the family learned of the patient's orientation; or another circle of individuals and relationships have now come to replace the biologic family. These issues need to be kept in mind in determining who can best speak for the lesbian or gay patient who lacks decision-making capacity.

EFFECTIVELY ENGAGING PATIENTS AND FAMILIES RELATED TO THEIR SPIRITUALITY AND RELIGION

The spiritual and religious beliefs of patients may influence lifestyle choices, be the bases for decision making, provide approaches for understanding and coping with illness and death and determine the rituals of death. For this reason, it is important to establish a pattern of clinical practice that conveys respect for and tolerance of the religious and spiritual beliefs of patients and their families. Many physicians, however, may be uncomfortable with or resistant to engaging patients and families around issues of spirituality and religion. This discomfort may be due to the "sensitive" nature of these issues or the physician's own personal ignorance, indifference, ambivalence, or nonbelief. Such obstacles are not surprising given the secularization of American society; increasing religious diversity in the United States due to immigration; and physician education and training that has emphasized natural, mechanistic, and scientific explanations for understanding and approaching disease. For the individual physician, this discomfort needs to be recognized and acknowledged to avoid aversive or dismissive behaviors that could undermine physician-patient communication.

In endeavoring to be respectful of spiritual belief and expression, the goal is to make reasonable efforts and provide good-faith accommodations that are patient centered and ultimately consistent with core professional values. In these efforts physicians should endeavor to be sincere in their

actions, while being authentic to their own spiritual beliefs. In this regard, it is certainly appropriate for the physician to refrain from doing or participating in something that she or he finds uncomfortable. However, as caregivers seek to become more culturally competent, physicians need to increase their comfort with, and capacity for, engaging patients and families around issues of spirituality. One of the simplest ways to demonstrate respect in this area is to early on inquire about spiritual or religious beliefs, issues, and concerns that are relevant and important to patient and the family. There is evidence, at least from outpatient settings, that such a question would not be unwelcome, although there may be racial and ethnic variations. This inquiry about spirituality can be initiated in an open-ended way by simply asking, "I can certainly imagine that this is a very stressful time. What do you rely on to get you through these very difficult situations?" A question such as this not only provides an approach for starting a conversation about spirituality, but it also allows the patient or family to give an answer with or without reference to religion or religiosity.

Other things that can be done as the opportunity arises, and where appropriate, include involving pastoral care, encouraging visits from the clergy of the patient's local congregation, and participating in patient/family-initiated ritual (e.g., prayer). The issue of physician-initiated prayer is controversial. Recognizing concerns over manipulation or exploitation of vulnerable patients, prayer, if initiated by the physician, must be (1) authentic for the physician; (2) welcomed by the patient; (3) respectful of the patient's beliefs; and (4) comforting, encouraging, and consoling.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 106

Sleep Deprivation and Sleepiness in Medical Housestaff and Appropriate Countermeasures

Indira Gurubhagavatula ■ Barry Fields ■ Ilene M. Rosen

In the past century, average sleep duration fell from 9 to just 7 to 7.5 hours nightly. Health care workers have not been immune to this trend. High-profile medical errors in the 1980s, along with a growing research base in the 1990s, bolstered claims of deterioration in physical and cognitive function among sleep-deprived physicians. Preventable adverse events cause 48,000 to 98,000 in-hospital deaths at a cost of $17 billion to $29 billion annually. The degree to which sleepiness causes these events remains uncertain, spurring sweeping reform in housestaff work hours and extensive research. A house officer without sleep for 24 hours has cognitive impairment similar to an intoxicated individual (blood alcohol concentration [BAC] of 0.10%). Given that intensive care units (ICUs) require continuous, 24-hour coverage and demand complex decision-making skills, addressing sleep deprivation and counteracting its effects in health care providers are of utmost importance.

Characteristics of Normal Sleep

Healthy human sleep is divided into four stages. Three are non-rapid-eye-movement (non-REM or NREM) stages (N1, N2, N3), whereas the fourth is known as rapid-eye-movement (REM) sleep. NREM sleep is characterized by progressive slowing of the frequency of brain wave activity detected by electroencephalography (EEG), with high-amplitude, slow waves (0.5 to 2 Hz frequency), also known as delta waves, predominating in N3 sleep. The major skeletal muscle groups remain active in NREM sleep. N1 is a transitional stage between wakefulness and deeper stages of sleep (N2 and N3). We spend 5% to 8% of sleep in N1, 45% to 65% in N2, and about 15% to 25% in N3.

Healthy sleepers spend about 20% of the night in REM sleep, which is characterized by a mixed-frequency, low-amplitude EEG that bears a striking resemblance to wakefulness. The major skeletal muscle groups are paralyzed, except for the eye muscles, diaphragm, tensor tympani, and posterior cricoarytenoid muscles. REM sleep periods occur in an ultradian rhythm, with the first REM onset occurring approximately 90 minutes after sleep onset. A typical first REM period may last for 20 to 30 minutes, with successive REM periods becoming longer and occurring at approximately 90-minute intervals. REM sleep therefore predominates the last third of the night, whereas NREM predominates the first third.

By contrast, the typical sleep pattern of a resident on call is characterized by frequent sleep interruptions because of calls regarding patient care. Overall sleep time is reduced, with disproportionately greater time spent in stage N1 and less in stages N3 and REM sleep. A delayed sleep onset time and early rise time also disproportionately reduce REM sleep. This fragmented, REM-deprived sleep pattern can lead to significant deficits in memory acquisition and performance of newly learned tasks.

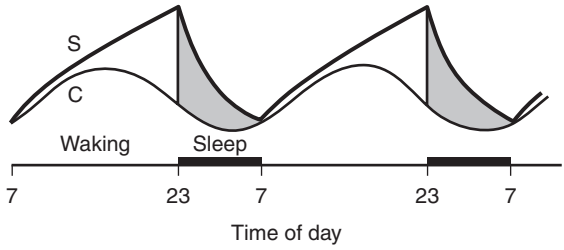


Figure 106.1 Two-process model of sleep regulation. Process S represents the homeostatic build-up of sleep pressure. Process C represents the circadian rhythm promoting wakefulness. Sleep propensity is greatest when the distance between process S and process C is at its maximum (solid vertical lines).

Measuring Sleepiness

Whereas *fatigue* or weariness results from prolonged physical or mental exertion, illness, or medications, *sleepiness* describes the tendency to fall asleep. Fatigue may improve with short breaks from work or rest without sleep, but sedentary conditions often unmask sleepiness. That is, a short break in a quiet room may alleviate the sense of fatigue in a medical resident, but make his or her sleepiness even more obvious.

Sleepiness can be measured using subjective tools, like the Epworth Sleepiness Scale. This 8-item, self-administered questionnaire quantifies sleepiness on a scale of 0 to 24, with a score > 10 representing sleepiness and a score > 15 suggesting pathologic sleepiness. Otherwise-healthy medical housestaff demonstrate Epworth scores well in the pathologic range.

Determinants of Alertness

An individual's level of alertness waxes and wanes throughout a 24-hour period. The greater the number of hours an individual spends awake, the greater the tendency toward sleepiness (Figure 106.1). This "sleep pressure," which dissipates after sleep, is known as the homeostatic "Process S." Process S is simultaneously counterbalanced by the circadian process, or Process C, which is driven by an internal clock residing in the suprachiasmatic nucleus. This wake-promoting internal clock operates with a periodicity of about 24.2 hours. A small circadian dip in alertness occurs in the late afternoon, and a larger nadir occurs at night, when the clock withdraws its wake-promoting signal. Because both Processes C and S favor sleepiness in the later evening and overnight, humans typically spend these hours sleeping.

Numerous external factors impact an individual's performance, including environmental factors, such as light, noise, and temperature; situational factors, such as immediacy and urgency, stress, or boredom; pharmacologic factors, such as the use of caffeine or other stimulants or alcohol; and individual factors, such as genetically determined tolerance to lower amounts of sleep. Despite these factors, if sleep need is not met, the homeostatic drive for sleep builds to the point at which the circadian system can no longer maintain wakefulness. As a result, the individual may experience micro-sleeps or sleep attacks despite attempts to stay awake. Indeed, firefighters have fallen asleep near burning wildfire embers because of the powerful homeostatic drive for sleep after several days of sleep deprivation.

Sleep-Related Determinants of Performance

Four characteristics of sleep determine performance: (1) nightly sleep duration; (2) number of hours awake; (3) perturbation of the circadian phase, as occurs when an individual works

nightshifts, and (4) sleep inertia. The third correlates with a misalignment of Processes C and S, as mentioned previously. Sleep inertia refers to the decrement in performance in the first 15 to 30 minutes after waking, with impairments observed in short-term memory, counting, cognitive processing speed, and number fact and lexical retrieval. These skills are critical for ICU residents, who may be awakened for emergencies and asked to synthesize, sort, and integrate voluminous data and deliver urgent decisions. Sleep inertia increases with the depth of sleep that precedes waking; hence, longer naps lead to sleep inertia more often than shorter ones.

Effects of Sleep Deprivation

Sleep deprivation results from insufficient sleep time, with neurobehavioral, cognitive, physiologic, and epidemiologic consequences. On a neurobehavioral level, microsleeps intrude into wakefulness involuntarily. Increased lapsing (errors of omission) and false responses (errors of commission) have also been described. Additionally, time-on-task decrements are observed, whereby the ability to sustain attention and respond quickly and accurately becomes unstable the longer an individual remains awake and attempts a repetitive task. Cognitive impairments are seen in learning and recall, working memory, and executive function. There is loss of the speed/accuracy trade-off: individuals take longer and still commit more errors with sleep deprivation.

Some individuals are far more vulnerable to cognitive deficits than others. Unfortunately, the ability of individuals to self-rate their degree of impairment tends toward inaccuracy; anesthesia residents misidentify EEG-confirmed sleep in 50% of trials. These effects can lead to workplace injuries. Indeed, concentration lapses and fatigue were the most commonly reported contributing factors among interns with percutaneous injuries. Such injuries were more frequent after extended shifts (mean of 29.1 consecutive work hours) versus non-extended shifts (mean of 6.1 consecutive work hours). Attention failures, medical errors, and personal injuries have been shown in sleep-deprived housestaff specifically during their ICU rotations.

Numerous physiologic perturbations of sleep deprivation include increased cortisol, cytokines, and C-reactive protein; leukocytosis; insulin resistance; on EEG, reduced sleep latency, increased slow waves, increased slow eye movements during sleep, and greater frequency of slow eyelid closures. Epidemiologic surveys reveal an increased likelihood of mortality, diabetes, insulin resistance, and cardiovascular disease in sleep-deprived individuals.

Performance decrements result not only from acute, total sleep deprivation, but from repeated nights of partial sleep loss as well, in a dose-responsive fashion. Therefore, a week of partial sleep deprivation, even without "extended" shifts, can result in more lapses than 2 consecutive days of total sleep deprivation.

Effects on Residents

Housestaff manifest lack of sleep in a variety of ways, with one of the greatest being the adverse impacts upon learning. In the critical care environment, housestaff must utilize both major categories of memory: procedural (knowing *how* to perform a specific task or surgical procedure) and declarative (knowing certain *facts* that can be applied to their patients). Sleep deprivation affects both types of memory adversely, impairing performance on in-training exams (declarative knowledge) and leading to procedures with more errors, unnecessary movements, and longer completion times.

Additionally, residents' satisfaction appears inversely proportional to the number of hours per week worked. Surgical residents actually report *less* operative participation while working within a more frequent call schedule, with more fatigue, increased stress, and decreased satisfaction.

Effects of the 2003 Duty Hour Restrictions

Before duty hour restrictions were implemented, 66% of post-graduate year (PGY)1 and PGY2 residents reported sleeping < 6 hours per night and 22% reported sleeping < 5 hours per night. The latter group was more likely to report working in an "impaired" condition, be named in a malpractice suit, use wake-promoting medications, be involved in serious accidents or injuries, make significant medical errors, or experience conflict with other professionals. These data led the Accreditation Council for Graduate Medicine Education (ACGME) to implement nationwide duty hour restrictions in 2003. These rules capped resident work to 80 hours/week (averaged over 4 weeks), limited call days to 24 hours (plus 6 hours for safe transfer of care), and mandated that 1 out of 7 days (average over 4 weeks) remain free of work-related responsibilities.

Subsequent survey data showed mixed rates of compliance by residents, with small reductions in weekly work duration. Noncompliance with ACGME standards was accompanied by increased risks of falling asleep while driving or stopped in traffic, motor vehicle crashes, depression, medication errors, and occupational risks including needle-stick injuries.

Two large observational studies adjusting for comorbidities, common time trends, and hospital site found no significant changes in mortality for medical or surgical patients in post-reform year 1. However, in post-reform year 2, the odds of dying decreased in teaching-intensive hospitals within the VA Hospital System for medical patients only. Nevertheless, improved outcomes have been difficult to confirm, given the relatively short time elapsed since the implementation and slow adoption of the ACGME standards.

Additional Countermeasures for Housestaff

Despite considerable debate and contradictory data as to the effectiveness of the 2003 ACGME duty hour restrictions at reducing house officer fatigue and improving patient safety, a new set of duty hour restrictions have supplanted them. Implemented in July 2011, these regulations are designed to foster "the professional responsibilities of physicians to appear for duty appropriately rested and fit to provide the services required by their patients." Interns may not work longer than 16-hour shifts, and upper-level residents may not work longer than 24-hour shifts. Since cognitive performance deteriorates after 16 hours of work, "strategic napping" should be encouraged; recent data suggest it leads to improvements in subjective alertness. Recognizing time constraints and recalling that sleep inertia is directly proportional to nap length, a 20- to 30-minute nap might allow one to return to work reasonably refreshed. If at all possible, that nap should coincide with natural circadian rhythms when sleep pressure is greatest; naps between 10 p.m. and 8 a.m. generally fall into that time frame (see Figure 106.1). Notably, driving during this period after an extended work shift without having taken at least a short nap is inadvisable.

Despite limited work hours and encouragement of napping, sleepiness will undoubtedly persist in clinical settings. Therefore, strategic use of wakefulness-promoting substances is another acceptable, albeit temporary way to combat these issues. Caffeine is the first-line pharmacologic intervention to improve vigilance and performance in sleepy individuals. Caffeine exerts the greatest effect on people who do not normally consume large quantities, with declining benefits in individuals who already do so. When consuming caffeine to remain awake, recall that the half-life of caffeine may exceed 6 hours in some individuals, so even one cup of brewed coffee (containing up to 200 mg of caffeine) may disrupt sleep onset and maintenance for many hours. Therefore, improperly timed overnight consumption can delay and degrade daytime sleep, which can be particularly problematic in nightshift workers.

Of course, these stopgap measures do not supplant sleep of adequate time and duration to ensure wakeful peak performance. The American College of Occupational and Environmental Medicine published a statement espousing the creation of a comprehensive "fatigue risk management system,"

which "manages employee fatigue in a flexible manner appropriate to the level of risk exposure and the nature of the operation." To this end, housestaff must make sleep a priority when they are not at work, whether day or night. Most adults require at least 7 to 9 hours of continuous sleep daily. Sleep should be attained in a dark, cool room free from pager chirps or text message alerts, and it should coincide with the body's normal circadian rhythm if possible. To combat nighttime shift sleepiness further (especially after several days of repetitive sleep loss), a short evening nap just before work can be another preemptive strategy to improve performance.

Conclusions

Whether implementing new duty hour restrictions will improve patient and provider safety is still unknown, but one immediate impact is a potential shift in workplace culture. These mandates send a message to the medical community and beyond that sleep health is a major priority. The ACGME requirements should serve as the backbone of the fatigue risk management system used by ICU trainees. Although these requirements pertain to the workplace, house officers' habits *outside* the ICU also impact performance and safety. Workplace sleepiness-mitigation strategies (napping and caffeine consumption) are useful adjuncts to, but not replacements for, a healthy home sleep schedule. Adequate sleep during time off is not a luxury but an essential strategy for handling workplace obligations responsibly and may improve health and safety among both house officers and their patients.

An annotated bibliography can be found at www.expertconsult.com.

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Patel SR, Ayas NT, Malhotra MR, et al: A prospective study of sleep duration and mortality risk in women. Sleep 27:440-444, 2004.

Women in the Nurses Health Study were observed over 14 years for sleep duration and mortality based on questionnaire data and the National Death Index. Nurses reporting 7 hours of sleep per night showed the lowest mortality, with higher mortality among nurses sleeping less than 6 or more than 7 hours per night, even after controlling for many health-related confounders. The study suggested that women are best served with 6 to 7 hours of sleep per night in terms of overall mortality. Reasons for increased mortality with sleep duration exceeding 7 hours could not be addressed in this cohort but may include undiagnosed sleep disorders.

Van Dongen HPA, Baynard MD, Maislin G, et al: Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. Sleep 27:423-433, 2004.

Healthy adults exhibited traitlike differences in susceptibility to the effects of sleep deprivation upon self-evaluated sleepiness, cognitive processing, ability, and sustained attention performance. The significant effects were remarkably stable through several intermittent periods of sleep deprivation within the same individual. These results support anecdotal accounts of varying vulnerability to sleep deprivation among intensive care unit staff.

Volpp KG, Rosen AK, Rosenbaum PR, et al: Mortality among hospitalized Medicare beneficiaries in the first 2 years following ACGME resident duty hour reform. JAMA 298:975-983, 2007.

This study closely mirrored that of Volpp et al in the Veteran Affairs (VA) population, but with Medicare patients in nonfederal hospitals before and after the 2003 ACGME duty hour restrictions. In this Medicare population, no mortality benefit was observed in any patient group regardless of diagnosis, hospital teaching intensity, or year since duty hour implementation. Closely analogous data will likely be available in future years to address the impact of 2011 ACGME duty hour restrictions on mortality.

Volpp KG, Rosen AK, Rosenbaum PR, et al: Mortality among patients in VA hospitals in the first 2 years following ACGME resident duty hour reform. JAMA 298:984-992, 2007.

Volpp and colleagues studied changes in mortality among U.S. Veteran Affairs (VA) hospital patients before and after the 2003 ACGME duty hour restrictions were implemented. They found no significant mortality changes during the first year of duty hour implementation, but the odds of dying decreased in teaching-intensive hospitals among medical (but not surgical) patients. These findings suggested that the benefits of duty hour implementation may be limited to specific contexts and could take longer than a year to materialize.

Volpp KG, Shea JA, Small DS, et al: Effects of a protected sleep period on hours slept during extended overnight in-hospital duty hours among medical interns: a randomized trial. JAMA 308:2208-2217, 2012.

In the first major study examining effects of "strategic napping" in medical housestaff, Volpp et al randomly assigned interns and senior medical students to a standard schedule (overnight shifts up to 30 hours) without protected sleep time or one with a protected sleep period from 12:30 a.m.–5:30 a.m. Participants in the latter group slept more and were more alert the next morning than those in the former.

Wells MM, Roth L, Chande N: Sleep disruption secondary to overnight call shifts is associated with irritable bowel syndrome in residents: a cross-sectional study. Am J Gastroenterol 107:1151-1156, 2012.

In this relatively large study (n = 205), medical residents were administered the ROME II questionnaire and the IBS-quality of life measure to elicit symptoms of the disorder. Hours of sleep deprivation during overnight call was associated with significant increase in IBS prevalence after adjusting for age and gender.

Wertz AT, Ronda JM, Czeisler CA, et al: Effects of sleep inertia on cognition. JAMA 295:163-164, 2006.

This study examined the quantification of the state of impaired cognition, grogginess, and disorientation that characterizes sleep inertia and compared it to sleep deprivation. Cognitive performance upon awakening in well-rested individuals was significantly worse than performance during a period of sleep deprivation. Severe cognitive impairment lasted for at least the first 3 minutes after awakening, creating a "sleep inertia" particularly detrimental to intensive care unit staff who must make quick decisions within minutes of awakening.

CHAPTER 107

Medical Errors and Patient Safety

Jeremy Souder ■ Jennifer S. Myers

The 1999 Institute of Medicine (IOM) report *To Err Is Human: Building a Safer Health System* estimated that 44,000 to 98,000 patients die annually in the United States as a result of medical errors. This report showed that errors in medicine were poorly understood and infrequently investigated, largely because of the culture of hospitals and the medical profession that saw these errors as the product of human failings. This belief led to a *person-focused approach* to error investigation, in which strategies to reduce medical errors involved censoring or re-educating staff about proper protocols and procedures. However, it is now known that this approach deprives organizations of the greatest opportunities for meaningful learning and improvement.

Since the IOM report, health care has increasingly been adopting a *systems-focused approach* to medical error. In this view, nothing is intrinsically different about medical errors as compared to errors in other complex, high-risk industries such as aviation or nuclear power generation. Like medicine, these fields rely heavily on human innovation and expertise to function normally, but long ago recognized that human errors are symptoms of deeper organizational problems. Like respiratory failure or heart failure, errors in medicine demand a diagnostic search for underlying causes and systemic repairs to prevent error recurrence.

This chapter presents a framework in which to understand, investigate, and prevent errors in the intensive care unit (ICU). These principles are widely used in the field of patient safety and can be applied to other areas of health care.

Key Patient Safety Concepts and Definitions

All health care organizations display characteristics of *complex adaptive systems*, in that they contain groups and individuals who have the freedom to act in unpredictable ways and whose actions are interconnected. High-performing, complex organizations follow three broad rules. First, *leaders give general directions* by articulating values, establishing a clear organizational mission, and setting objectives. Second, *resources and permissions are provided to the appropriate personnel* within the organization, and they are incented to efficiently and safely fulfill patient needs. Finally, organizational *constraints* prevent providers from giving inefficient or unsafe care.

These three rules are expressed through organizational structures and processes. *Structures* are the organizational and management hierarchy, physical facilities, staffing, and capital allocated to perform a process. A *process* is the way humans and other resources interact to deliver patient care. Together, the structure and process creates the final products of health care, which are referred to as *outcomes*.

An error is a defect in process that arises from a person, the environment in which he or she works, or, most commonly, an interaction between the two. In the field of patient safety, negative outcomes are termed *adverse events.* Because patients may experience adverse events as a result of their underlying illnesses, *preventable adverse events* are differentiated from *unpreventable* adverse

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events; the former are due to error, whereas the latter are not. Errors that do not result in patient harm are termed *near misses* and are more common than adverse events. Safety experts understand that near miss events are equally useful to study to prevent future errors. Table 107.E1 illustrates the difference between these terms.

Errors in Complex Systems

Errors in complex systems can be divided into two types based on where they occur in the system. *Active failures* occur at the *sharp end* of a complex system, so named because it contains the people and processes that are easily identified when an adverse event occurs because of their proximity to the patient and the harm. Active failures always involve a *human error,* such as an act of omission (forgetting) or commission (misperceptions, slips, and mistakes). Research done in human factors has shown that the incidence of human error is predictable based on the nature of a task, the number of steps in a process, and the context in which these occur. Table 107.E2 provides examples of these types of errors. Although active failures are easiest to identify, they represent the tip of the iceberg and nearly always rest on deeper and more massive latent conditions in the organization.

Latent conditions are defects in a system that make it error-prone. Arising from the physical environment and as unintended consequences of decisions made by organizational leaders, managers, and process designers, latent conditions are the unforeseen *blunt end* of a system that has "set people up" to fail at the sharp end. Indeed, the majority of near misses and preventable adverse events identify multiple causative latent conditions. For example, consider an investigation of a central line–associated bloodstream infection in the ICU. Several potential latent conditions for this infection are listed in Table 107.E3. Note that if this investigation had focused on active failures alone, it would have stopped short and blamed providers without identifying the underlying latent conditions that allowed the error or preventable infection to occur.

Latent conditions breed human error through a variety of factors. *Knowledge factor* impairment makes an individual's impression of what is happening inaccurate or incomplete. An example would be an intelligent intern struggling to apply extensive prior "book learning" in the context of actual clinical practice. Excessive mental workload, fatigue, and distractions make it difficult to focus *attention* and maintain an accurate overview of the complex situation at hand, also known as *situational awareness*. One example of the latter is the difficulty that an ICU physician may have in remembering to order and follow up on coagulation factors every 6 hours for a patient on heparin while simultaneously managing multiple other critically ill patients. Impaired attention also increases the use of *heuristics,* which are the cognitive shortcuts we use to increase mental efficiency during times of stress. Although they may increase productivity in the short term, heuristics also increase certain types of human errors. Lastly, *strategic factors* force providers into difficult trade-offs between opposing objectives when time and resources are limited and risks and uncertainties abound. An example would be deciding whether or not to give the last open ICU "crash" bed to a medical/surgical floor patient who is hemodynamically stable, but difficult to manage on the floor because of observation or monitoring demands.

Figure 107.1 illustrates that on one side, the expression of human error or expertise at the sharp end is governed by the evolving demands of the situation being managed and on the other side by the organizational context in which an individual is operating. Organizational structures and culture at the blunt end of the system determine what resources and constraints people at the sharp end experience, powerfully influencing how well they will be able to use their knowledge, focus their attention, and make decisions during the course of their work (see Figure 107.1).

TABLE 107.E1 ■ **Patient Safety Terms and Examples**

Term	Example
Adverse event	A patient is administered heparin and develops HIT
Unpreventable adverse event	A patient who has no known history of HIT is administered heparin and develops HIT
Preventable adverse event	A patient with a known history of HIT is administered heparin and develops HIT
Near miss	A patient is prescribed heparin, but before drug administration the pharmacist notes that the patient has a history of HIT and calls the doctor to cancel the order before it reaches the patient

HIT, heparin-induced thrombocytopenia (see Chapter 45).

TABLE 107.E2 ■ **Human Error in Active Failures: Types and Examples**

Type of Error	Example
Omission—forgetting	Physician forgets to order heparin for DVT prophylaxis.
Commission—misperception	Physician recalls patient had recent history of severe hemorrhage (when in fact it was an otherwise similar patient the physician had admitted the same night after being roused from sleep) and therefore does not order heparin for DVT prophylaxis
Commission—mistakes	Physician notes mild thrombocytopenia and thinks it is a contraindication to heparin for DVT prophylaxis, so heparin is not ordered
Commission—slips	Admitting physician believes he or she has ordered heparin DVT prophylaxis and has actually done so—but for the wrong patient

DVT, deep venous thrombosis.

TABLE 107.E3 ■ **Latent Failures: Domains and Examples Related to a Central Line Infection**

Domain of Latent Condition	Example
Policies, procedures, and processes	Absence of a standardized, evidence-based approach to central line insertion or maintenance
Information systems	Lack of documentation or access to documentation related to timing and observation of dressing changes
Materials and equipment	Unavailability of chlorhexidine or dressing kits needed for central line maintenance; changes of line kits without education of personnel regarding how to use new kits
Work environment and architecture	Insufficient lighting or room setup made sterile central line insertion and maintenance difficult

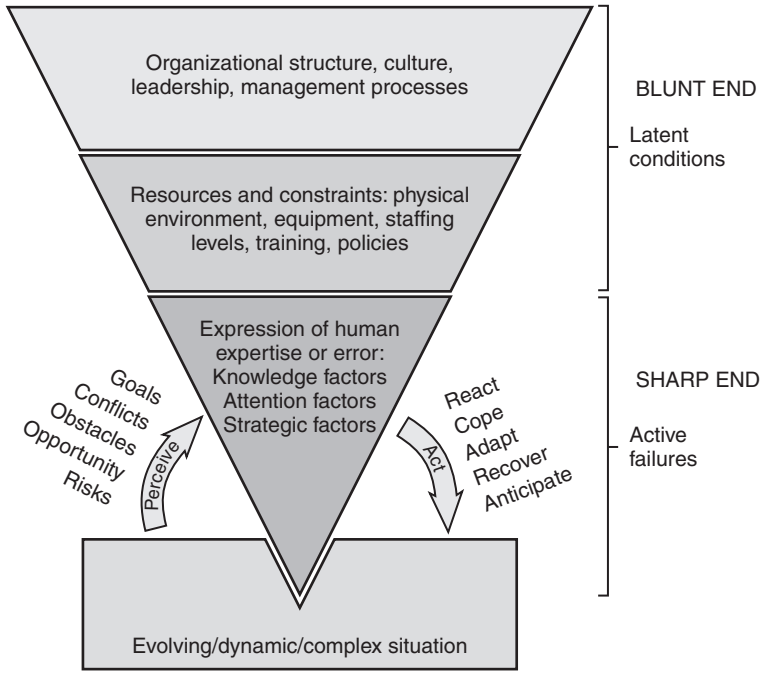


Figure 107.1 Sharp-end operators mediate the interaction between evolving work situations and the organizational context (structures and processes). Factors at the blunt end markedly influence the likelihood that an operator will express human expertise or human error. *(Based on an image from Woods DD, Dekker SWA, Cook RI, et al: Behind Human Error, 2nd ed. Aldershot, UK: Ashgate, 2010.)*

Tools for Error Analysis in the ICU

Root cause analysis (RCA) is a widely used patient safety tool. In this *retrospective* analysis, latent conditions, or "root" causes of an error, are identified through a deliberate process that explicitly moves past proximal, seemingly obvious active failures. In an RCA, a facilitator leads a multidisciplinary team through a review of the event to uncover system failures in an open environment that explicitly avoids assigning blame.

Diagrams are often used in or created from a root cause analysis, and they can help demonstrate the relationship between the various factors that contributed to an error or unanticipated event. Figure 107.2 shows a cause-and-effect diagram for an ICU patient who suffers a gastrointestinal bleed related to a heparin dosing error. A discussion focused on active failure would spend time talking about why the physician ordered the wrong heparin dose. A root cause analysis would identify multiple contextual factors and latent conditions that allowed this error to occur.

In addition to dissecting the medical error, RCA teams create action plans for improvement, assign responsibility for those improvements, and consider metrics that allow the organization to measure the results of the intervention. *Failure Modes and Effects Analysis (FMEA)* is a highly structured, *prospective* method in which a process is studied to determine what types of errors may result from its operation in the system and what *effects* or outcomes the error is likely to cause. The likely effects of a failure are prioritized according to their severity, frequency, and detectability. This detailed analysis is then used to develop countermeasures and redesign the process to make it more reliable. Other important tools for patient safety include leadership walk rounds with frontline staff to observe and learn more about real-world operating conditions and safety

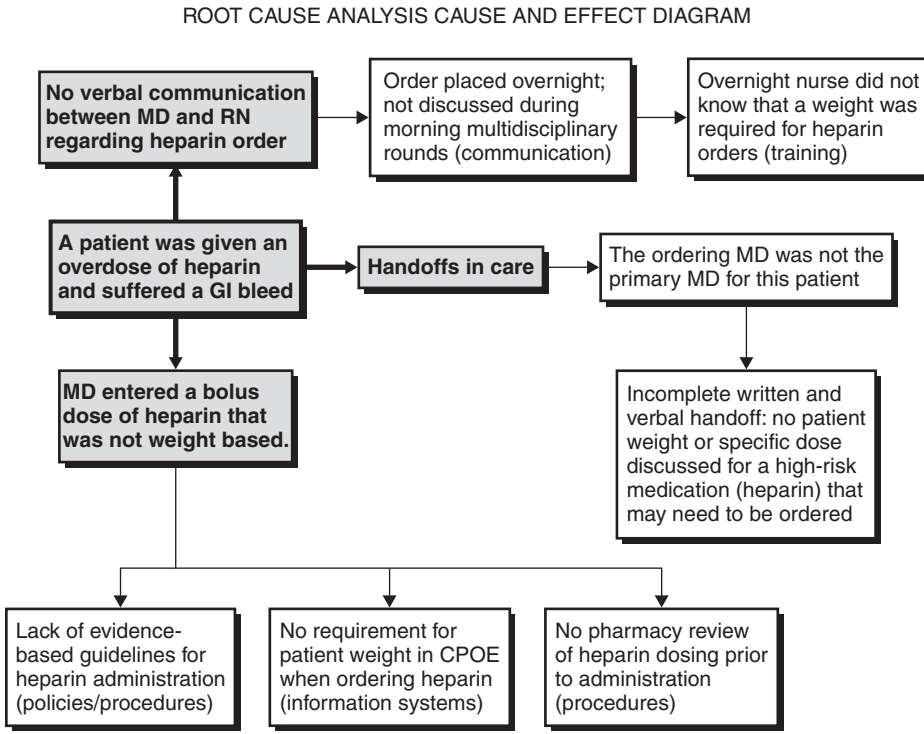


Figure 107.2 Cause-and-effect diagram for heparin medication error causing patient harm. GI, gastrointestinal; CPOE, computer physician order entry system

concerns and the use of easily accessible incident reporting systems to promote reporting of near misses and other adverse events. Key to each of these is subsequent follow-up and action, with feedback to and recognition of the frontline staff who have participated in identifying problems. Each of these activities facilitates a culture of safety (discussed later).

Error Disclosure

There is always an ethical duty to disclose an error to a patient when it results in harm. Nonetheless, multiple barriers to disclosure remain in health care, including the profound negative emotions that physicians experience when their patients are harmed by an error, including guilt, fear, anger, remorse, and isolation. Complicating these emotions, many physicians are unsure of what to say and how to say it given the fear of litigation. Addressing these factors can help alleviate the emotional barriers.

To maintain the trust of patients and their families, errors should be disclosed as soon as possible after the event has occurred. The person that the patient identifies as being responsible for his or her care should make the disclosure. This is usually the most senior physician but may vary depending on the clinical circumstances. For example, an intensivist would most likely disclose an error in the ICU. However, if the error were related to a surgical intervention that occurred while the patient was in the ICU, it may best be disclosed by the surgeon or collaboratively by both the intensivist and the surgeon. Additional information on this topic can be found in Chapter 109.

Conclusion: Establishing a Culture of Safety in the ICU

A *culture of safety* is critical to reducing errors and improving ICU performance and is characterized by a pervasive preoccupation with identifying and preventing error. Culture is formed by the attitudes and behaviors of the people who work in a particular area as well as their leaders. A critical precondition for a culture of safety is a *just culture,* in which front-line individuals are held accountable for competent performance, but not the shortcomings of the organization in which they work. Clinicians have a readily accessible incident reporting system and know that they will not be punished for using it to report safety concerns. Once established, health care providers at all levels in the organization can share accountability for safe, reliable care; feel safe themselves when reporting problems, near misses, and errors; and have the forum and expectation to do so. The analysis of reported incidents and problems generates information that these providers and their leaders can use to improve patient care.

In other complex industries, organizations that consistently maintain safe performance by fostering the principles outlined here are termed *high-reliability organizations.* These organizations articulate their safety objectives clearly, recognize that people are the preeminent guardians of the system, and are preoccupied with learning from errors and creating effective error-reduction strategies. The challenge for medicine is to learn from the success of high-reliability organizations and adopt their principles in order to achieve the highest levels of safety in our field.

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CHAPTER 108

Medical Malpractice, Risk Management, and Chart Documentation

Jason B. Turowski ■ Scott Manaker

Although intensive care unit (ICU) physicians aim to "do no harm," at times undesirable outcomes happen beyond one's control or as a result of error. This chapter introduces malpractice suits and their origins. It also discusses the management of untoward outcomes in the ICU in the context of medical errors and risk management related to chart documentation, especially the impact of the electronic medical record (EMR).

Origins of Malpractice

Malpractice litigation transcends courtrooms, juries, and money; it embodies several social goals. These goals include compensating patients injured from negligence, attempting to make them whole again; exacting corrective justice, aspiring to bear the costs of reparation; and deterring unsafe practices by creating economic incentives for precaution, as it would appear less expensive to avoid mistakes than to make them.

In reality, malpractice suits do not achieve these laudable social goals, as only some patients injured from negligence receive compensation. Approximately 70% of malpractice cases resolve before ever going to trial, and only 30% of cases close with payment to plaintiffs. Claims are brought against both negligent and non-negligent physicians, and acting negligently does not guarantee a claim will be brought as most errors do not precipitate a subsequent malpractice suit. A deterrent effect of malpractice remains unproven. Instead, many posit that malpractice suits may prompt defensive medicine that increases health care costs. Others perceive that, rightly or wrongly, the current tort system is fair to plaintiffs and emphasizes individual accountability for both the physician and the patient. The system overall seems inconsistent in distributing compensation and exacting justice, with inherent inefficiencies resulting from high administrative costs.

The doctor has a *duty* or a responsibility to a patient to perform a particular service, when treating sepsis, providing mechanical ventilation, or managing routine critical care. A provider may fail to meet the *standard of care* for a particular service as a result of an error or by gross negligence. Medical *malpractice* requires an injury derived from a deviation in the applicable *standard of care*.

For intensivists, the standard could be to relay critical information in a timely fashion to the patient (the family or health care proxy); educate the patient or his or her surrogate on what the critical information means; offer viable options to address the imminent health care issue; and explain the risks, benefits, and alternatives of therapy. The applicable standard of care may be a local/regional or national definition, based on individual state laws and regulations. For specialists, such as intensivists, a national standard is typical.

The standard of care is defined as a quality of care that would be expected of an ordinary or reasonable physician in the same specialty in a similar circumstance, but not necessarily in the same locality. Trainees such as residents and fellows are *not* held to the same standard as attending

physicians in their respective specialties. Although jurisdictions vary, in general, attendings are indirectly liable for the negligence of residents working under their supervision, and directly liable for inadequate supervision of residents who commit error. A greater than 50% probability ("more likely than not") defines *negligence* and the medical *standard of care*, a lower threshold of proof than the "beyond a reasonable doubt" (< 90% to 95%) standard used in criminal litigation. Furthermore, the defendant physician owes a duty of care to the plaintiff patient. A malpractice allegation contends that the defendant breached that duty by failing to adhere to the standard of care, resulting in injury to the plaintiff.

Why Are Intensivists Sued?

Poor communication between a physician and a patient or patient's family can frequently lead to litigation (Box 108.1). Most medical malpractice cases do not involve actual negligence. Beckman et al reviewed 45 plaintiffs' depositions, selected randomly from 67 lawsuits in 1985-1987, all against a large city hospital. The decision to litigate was most often associated with a perceived lack of caring and lack of availability on the part of the practitioner being sued. Additional factors also contribute to the decision by a plaintiff to proceed with a malpractice suit (Figure 108.1).

BOX 108.1 ■ Contributing Factors to the Decision to Pursue a Malpractice Suit

Why a Plaintiff Sues

- Has been advised by doctors or other trusted colleague to sue
- Has financial needs
- Believes there is no future because of the injury
- Wants an explanation for the injury
- Seeks revenge
- Is dissatisfied with physician-patient communication

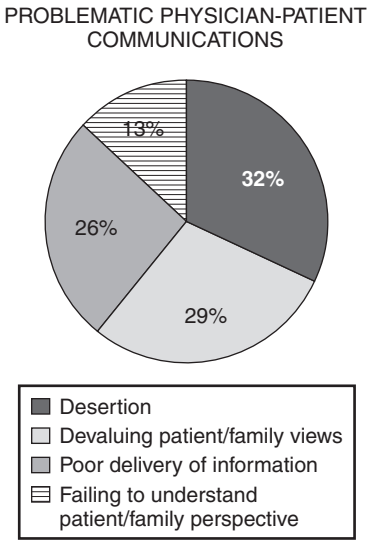


Figure 108.1 The four general categories of issues expressed by plaintiffs and their relative prevalence in the two thirds/three quarters of malpractice suits that were judged to have arisen due to problematic interpersonal relationships. *(Data from Beckman HB, Markakis KM, Suchman AL, et al: The doctor-patient relationship and malpractice: lessons from plaintiff depositions. Arch Intern Med 154:1365-1370, 1994.)*

Medical Malpractice and the Chest Physician

Physicians from medical disciplines that perform the most procedures generally have the most medical malpractice claims. The concept of *res ipsa loquitur*, "the thing speaks for itself," means that the plaintiff must prove that an injury could not have occurred absent negligence, could not have been caused by the plaintiff, and was under the defendant's control. Fulfilling this concept then burdens the defendant to prove that negligence did not occur. An adverse event or outcome following a procedure is enough evidence to convince a jury that negligence has occurred. Five major allegations (Box 108.2) in malpractice suits that generally apply to most physicians, including nonproceduralists, certainly apply to intensivists.

Errors in the Intensive Care Unit

The ICU environment also lends itself to high rates of iatrogenic events and medical errors (MEs), with overall ME rates estimated at 2.1/1000 patient days (see Chapter 107). Up to 10% of ICU patients will experience at least one ME. The most frequent MEs surround insulin administration (as high as 186 MEs/1000 days of insulin therapy), paralleling the prominence of this medication (along with anticoagulants) in studies of medication error rates. Vasopressor/vasoactive medication administration errors are also highly prevalent, as are MEs and complications associated with mechanical ventilation. The frequent MEs associated with mechanical ventilation include unplanned extubation, overinflation of the endotracheal cuff balloon, and failure to elevate the head of bed (> 30 degrees).

Adverse events in the ICU may result in one or more clinical consequence(s), requiring one or more procedures or treatments. Experiencing two or more adverse events represents an independent risk factor for mortality in the ICU. Mortality resulting from MEs suggests an urgent need to continue developing ME prevention programs, from the patient safety and patient-centered care perspectives (see Chapter 107). Ideally, these programs should dovetail with improved communication strategies, such as including families on rounds and encouraging family meetings to discuss goals of care and options/limitations/withdrawals of care (see Chapters 102, 104 and 105).

MEs are known to be underreported, with complicated and varying definitions of what constitutes error. These general characteristics equally apply in the ICU. Underreporting has been ascribed to fear of retaliation or retribution, combined with insufficient emphasis on patient safety, leading to inadequate motivation of staff and absence of feedback about the effect of medical error (see Chapter 107).

Electronic Medical Records (EMRs)

A health care system empowered by information technology (IT) must also recognize the associated potential risks. These risks include physician liability, breaches of privacy and confidentiality, ownership of data, and potential adverse effects on the quality of care and clinical practice guidelines. Core features of an electronic medical record (EMR) may include provider clinical

BOX 108.2 ■ Top Five Causes of Malpractice Suits

Reasons Medical Practitioners Are Sued
- Errors in diagnosis
- Improper performance of a procedure
- Failure to supervise or monitor care
- Medication errors
- Failure to recognize complications

documentation, patient demographics, diagnostic testing results, order entry, and, ideally, clinical decision support based on widely accepted practice guidelines. Implementation of EMRs may initially increase rather than decrease malpractice suits. Errors or adverse events may result from individual mistakes or system-wide failures. Gaps often occur during the transition from paper to electronic documentation. Partial implementations, where care is rendered partially with paper records and partially with an EMR, can produce higher error rates than either a complete EMR transition or maintaining existing paper processes.

Some experts believe EMRs will eventually decrease liability, and several insurers have offered discounts to providers who have switched to EMRs. But optimistically, numerous salutary effects of EMRs should accrue, such as potentially fewer harmful errors, with limited test duplications. More complete (and legible) patient documentation, with fewer transcription errors, should result from use of an EMR. EMRs provide more timely access to more complete patient health information, interoperability barriers notwithstanding. Most important, EMRs offer the promise of improved communication, with facilitated decision making and guidance. Better adherence to clinical guidelines and reduction in rates of medication errors has been suggested, but without compelling evidence that EMRs reduce diagnostic errors.

EMRs do have their problematic attributes as well. Automatic discontinuation of medications can occur, particularly at the time of transfer to or from the ICU, when careful medicine reconciliation is necessary. Defaulting to potentially dangerous drug doses may happen, as system software fails to cross-reference current clinical status with prior known values of renal or liver function. Easy access to copious prior records tempts providers to rely on prior history, physical exam, and other data without taking the time to collect new and verify the old information. The "copy and paste" functions of text editing may perpetuate earlier errors.

EMRs could complicate the course of malpractice litigation. First, EMRs increase the volume of information contained within a medical record, which must be evaluated to defend or prosecute a claim. Access logs also known as *metadata* provide a written trail of exactly when a provider reviewed the EMR, which portions of the record were reviewed, and what entries were made. Importantly, these metadata constitute a permanent electronic footprint of activity in the EMR and can be utilized to authenticate electronic entries, thus rendering falsification of data virtually impossible in today's electronic age.

Electronic Medical Records and the Standard of Care

To prove malpractice, a plaintiff must establish that a deviation below the applicable standard of care caused an injury. With their rapid pace of implementation, adoption, and evolution, EMRs may shape medical liability both by altering the way courts determine the standard of care and also by actually changing the standard itself. Clinical decision support tools, widely touted as a method to improve the quality of care and reduce both MEs and variability, may drive this change by assuming many attributes of clinical practice guidelines. In the course of litigation, explanations for why decision support was (or was not) created to address a specific issue may become part of the substance of the case, as well as an individual provider's history of accepting or ignoring such advice. A court may admit clinical decision support systems as evidence of the standard of care, if an expert attests that these systems reflect reasonable and customary care. Yet such clinical decision support needs to be tailored to the needs of an individualized patient as part of patient-focused care, such as balancing the benefits of anticoagulation or antiplatelet therapy with the risks of gastrointestinal bleeding.

The proliferation of health information exchanges (HIEs) with accessibility to external medical records may also change the standard of care. Previously, little duty existed to comprehensively obtain or review prior records, absent an easy way to consider them in the context of critical care. With massive quantities of potentially accessible electronic data, the applicable standard may

evolve to include large-scale review of these data and transformation into clinically actionable decision making in the ICU. Successful evolution of functional HIEs may create new expectations and standards for access to such clinical information.

Clinical Pearls

1. Reduce MEs with systematic approaches to delivery of critical care (see Chapters 103, 107 and 111).
2. Practice frequent, effective communication with patients and families (see Chapters 102, 104, and 105).
3. Clearly document into the medical record thoughts and considerations culminating in important clinical decisions. Describe errors and adverse events in a lucid and factual, but not blameful or accusatory, manner. Cite the participation of patients and their families in ICU discussions and decisions, and the content of those conversations, in the medical record.
4. Effectively balance the use of "cut and paste," pull forward, macros, and other text editing tools for efficiency with recognition of personal responsibility for the veracity of such information. Accurately update and personalize such notes to demonstrate the patient-centered care being delivered in real time.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 109

Long-Term Acute Care in the Spectrum of Critical Care Medicine

Michael A. Grippi ■ Michael J. Soisson

With implementation of the Medicare inpatient prospective payment system (IPPS) in the early 1980s, the Health Care Financing Administration (now the Centers for Medicare and Medicaid Services, CMS) and acute-care hospitals identified a need for alternative care settings for patients who did not easily fit into the reimbursement system developed under diagnostic related groups (DRGs). As a result, three categories of facilities were established as exempt from the DRG payment system: inpatient rehabilitation facilities, inpatient psychiatric facilities, and long-term acute-care hospitals (LTACs). These facility categories were paid originally under a "cost-based" model, enacted through the Tax Equitable Fiscal Responsibility Act (TEFRA) of 1982.

The modern LTAC was developed as a lower-cost alternative to the patient staying in an intensive care unit (ICU) and has evolved into a facility specializing in the care of medically complex patients—that is, patients who survive the initial phase of their acute and often catastrophic illness and are in need of additional care for several weeks or longer. Not unexpectedly, LTACs have focused on patients requiring long-term mechanical ventilation—a challenging group with historically long lengths of stay in the ICU.

Evolution of Long-Term Acute Care and the LTAC Hospital

Evolution of the LTAC occurred in three relatively distinct phases. The original LTACs date back to the early 1920s and comprised facilities focused principally on the chronic care of patients with tuberculosis, rehabilitation of adults and children with disabilities, and treatment of psychiatric disorders. LTAC developed in response to community needs for physically and psychologically challenged citizens, and they were run primarily by philanthropic organizations. The initial LTACs were large (65 to 100 beds) and freestanding, and often incorporated a long-term residential component.

In the 1980s and early 1990s, "weaning hospitals," which were based on an extension of principles derived from facilities caring for individuals with tuberculosis, focused on patients who required significantly longer stays than those for which the IPPS was designed—namely, patients requiring respiratory care and ventilator weaning. These typically freestanding LTACs were large enough to support small hospital operations, including meal service, physical therapy, and administrative and financial systems. Many were built and operated by a limited number of for-profit companies using private or investment equity. Designed as regional centers aimed at drawing patients from several acute-care hospitals, these early "weaning hospitals" were located in proximity to acute-care referral sources. These facilities also spawned growth of for-profit, specialty hospital chains.

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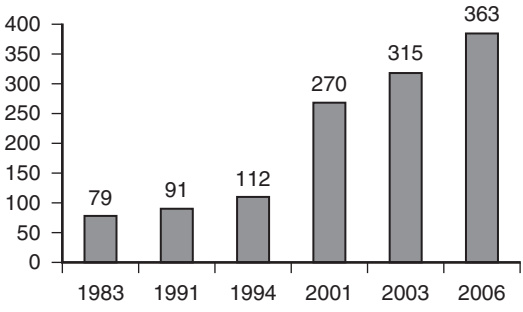


Figure 109.1 Growth in the number of LTACs over three decades.

TEFRA in 1982 created an alternative payment system for Medicare patients managed in LTACs, exempting these facilities from the IPPS. LTAC reimbursement under TEFRA was based on the average cost per discharge, and it established incentives for acute-care hospitals to transfer complex, "chronically critically ill" patients to LTACs. This incentive to shift high-cost Medicare patients to facilities paid on a cost basis triggered a dramatic increase in the number of LTACs from under 100 in 1990 to over 360 in 2005. Although the earliest organizations were largely not-for-profit, by 2004, for-profit organizations predominated. Currently, only two companies own two thirds of for-profit LTACs.

The most recent phase in LTAC evolution is based on the concept of a "hospital within a hospital." As the IPPS translated into reduced lengths of stay in acute-care hospitals, excess bed capacity arose, and the number of Medicare patients requiring longer stays (because of medical complexity) remained high. In response, several hospital chains creatively proposed "lease agreements" to acute-care hospitals, under which an LTAC rented space within an acute-care facility that had excess bed capacity. As a result, the acute-care hospital was paid for unused space and reimbursed for clinical and ancillary services provided to the LTAC. In addition, the acute-care hospital could move its longer-stay (and, hence, higher-cost) Medicare patients to "another facility." By locating within an acute-care hospital, the LTAC administrative staff achieved significantly lower operating costs, maintained access to the acute-care hospital's medical staff, and readily identified a pool of potential referrals.

In concert with development of the "hospital within a hospital" concept, escalating costs of critical care prompted attention on patients who were "outliers" in the ICU under the IPPS. Most "outlier" patients were ventilator dependent and difficult to wean, thereby generating excess cost. Therefore, an alternative, less expensive site of care was sought.

After nearly 20 years of continuously escalating costs, in 2003 Medicare initiated a prospective payment system for LTAC facilities. Based on "long-term care diagnosis-related groups" (LTC-DRGs), payment to an LTAC is now tied to the patient's principal diagnosis. Currently, more than 975 LTC-DRGs exist. Despite the implementation of LTC-DRGs attempting to manage escalating costs, the number of LTACs has increased further to nearly 400 (Figure 109.1). Medicare expenditures to LTACs have also ballooned to an estimated $5.27 billion in 2007. In 2008, CMS froze payments at the 2007 rate, and the agency is presently considering other cost containment measures, including a 3-year moratorium on new LTAC hospital beds.

Geographic Distribution of LTACs

For unclear reasons, a unique geographic distribution of LTACs has evolved. Unlike the case for post-acute facilities, characterized by a fairly homogeneous distribution of inpatient rehabilitation or skilled nursing facilities across the country, LTACs appear highly concentrated in certain regions. In particular, LTAC facilities predominate in the northeastern and southern parts of the

United States, with 35% of all facilities in three states (Massachusetts, Louisiana, and Texas). Northern states have the majority of the older hospitals; most of the newer, respiratory-based facilities are in southern states. A variety of factors related to the origins of these hospitals, state-specific legislation relating to certification of need, and unique demographics may account for this significant variability in distribution.

CMS has long expressed interest in drawing conclusions regarding the clinical value of LTACs based on this geographic heterogeneity and questioned where patients deemed appropriate for LTACs are receiving such care in areas without LTAC facilities. Despite significant research on the basis for the heterogeneity, few solid conclusions have been drawn.

Startup Requirements

Medicare certification for an LTAC requires that the prospective facility first meet state licensing requirements as an acute-care hospital. In addition, the facility must prove that it meets Medicare's "LTAC Conditions of Participation" during a 6-month demonstration period. Prior to 2007, these conditions made up the critical requirement that the facility have an *average* length of stay for Medicare patients of 25 days or greater, and achieve Medicare certification for an acute level of care through a CMS Medicare survey.

However, the signing of Medicare and Medicaid State Children's Health Insurance Program (SCHIP) legislation in 2007 resulted in CMS expanding LTAC certification requirements to include (1) a preadmission patient review process that screens for the appropriateness of admission, as well as validation (within 48 hours of admission) of the need for LTAC admission; (2) a concurrent review process that evaluates the patient's need for continued stay in the facility; (3) documentation of active physician involvement in patient care, with daily, onsite physician presence and the availability of consulting physicians who can be at the patient's bedside in a "moderate period of time"; and (4) documentation of an interdisciplinary treatment plan for each patient.

For reimbursement purposes, during the demonstration period, Medicare treats the facility as a short-term acute-care hospital (in some cases, the facility may be certified as a rehabilitation facility) and pays the prospective LTAC under the IPPS. Based on this reimbursement model, most LTACs suffer significant payment shortfalls during the demonstration period and attempt to keep Medicare patient volumes as low as possible in order to minimize the negative financial impact.

For many facilities, management of the length-of-stay requirement and expected initial financial losses are significant challenges. In addition, new facilities must develop core clinical competencies, build their medical staff, and manage patients who are medically complex, yet stable enough to remain in the evolving LTAC setting. Failure to achieve the Medicare length-of-stay requirement during the demonstration period requires the facility to refile its Medicare LTAC application and begin a new 6-month demonstration period—a process that can begin only at the start of the facility's cost report year.

Because Medicare has been the primary payer for LTACs, attempts are ongoing to define and clarify the clinical and financial values of LTACs to CMS. Indeed, patients covered by Medicare constitute approximately 65% of those admitted to LTAC facilities.

Current Medicare Rules Governing Reimbursement for LTACs

LTACs and CMS legislative rules have undergone unprecedented change since implementation of the LTC-DRGs, including the final rules issued by CMS for rate year 2008 and the SCHIP Extension Act of 2007. LTC-DRGs have rigid expectations regarding length of stay, case weights, and cost outlier thresholds. Although the Medicare reimbursement model is relatively simple

for most cases, a number of complicated formulas adjust payment if the patient fails to meet the expected length of stay associated with each DRG.

Despite the relatively complicated conditions of Medicare participation, properly managed LTACs can provide valuable, cost-effective care. Because of a longer length of stay, LTAC patients recover and rehabilitate over a slower time frame. Furthermore, the concentration of patients with similar clinical issues allows an LTAC to develop comprehensive treatment protocols.

Patient Populations in the Long-Term Acute-Care Environment

Based on Medicare data, respiratory-related diagnoses (including the use of mechanical ventilation) constitute the most common LTC-DRGs (Table 109.1). In 2007, approximately one quarter of Medicare-based discharges from LTAC facilities were categorized as respiratory-related DRGs, including 10.6% that were related to chronic ventilator support.

The remaining mix of DRGs (Table 109.1) includes degenerative neurologic disorders; nonhealing wounds in patients who have poor nutrition or who have been bedridden at home or in long-term care institutions; and postsurgical complications, including nonhealing surgical wounds, renal failure, or multisystem organ failure. In addition, candidates for an LTAC include deconditioned patients who require slower-paced rehabilitation and who cannot tolerate the required 3 hours of therapy in an acute inpatient rehabilitation facility.

TABLE 109.1 ■ **List of Most Frequent Diagnosis-Related Groups (DRGs) for Long-Term Acute-Care Hospitals (LTACs) in 2004**

Clinical Descriptor	Number of Discharges	Percentage
Respiratory system diagnosis with ventilator support	13,007	10.6
Aftercare, musculoskeletal system and connective tissue	6212	5.1
Degenerative nervous system disorders	5802	4.7
Skin ulcers	5594	4.6
Rehabilitation	5072	4.1
Chronic obstructive pulmonary disease	4980	4.1
Pulmonary edema and respiratory failure	4960	4.1
Simple pneumonia and pleurisy with complications/comorbidities	4826	3.9
Aftercare without history of malignancy as secondary diagnosis	4497	3.7
Respiratory infections and inflammations with complications/comorbidities	4449	3.6
Septicemia	4144	3.4
Skin graft or debridement for skin ulcers with complications/comorbidities	3739	3.1
Heart failure and shock	3699	3.0
Renal failure	2360	1.9
Psychosis	2355	1.9
Total Discharges	**122,320**	**61.9**

From MedPAC Report to the Congress: Medicare Payment Policy, March 2006.

Clinical Outcomes

The literature on clinical outcomes in LTACs is not robust. The relative paucity of studies focuses primarily on weaning success rates. In general, one third to two thirds of ventilator-dependent patients admitted to LTACs are liberated from mechanical ventilation. Only about 50% of Medicare patients ≥ 65 years old who were admitted to an LTAC after critical illness remain alive in 12 months.

Medicare focuses on three types of quality measures for LTACs: mortality rate, readmission rates to acute-care facilities, and selected patient safety indicators from the Agency for Healthcare Research and Quality (AHRQ). Patient safety indicators include the incidence of pressure (decubitus) ulcers; rates of nosocomial infections; and incidences of postoperative pulmonary embolism, deep venous thrombosis, and postoperative sepsis. Clinical outcome measures include rates of liberation from mechanical ventilation, incidence of ventilator-associated pneumonia, nosocomial infection rates, rates of discharge to home, functional improvements, and improvements in severity of illness.

An annotated bibliography can be found at www.expertconsult.com.

Challenges for LTACs

Like all health care organizations, LTACs will face a number of challenges as they continue to evolve. One major challenge is that, despite the best efforts of many providers, the very existence of the facilities is predicated on considerations of reimbursement, rather than quality of clinical care. From the perspective of the federal government, LTACs are paid differently solely because they do not fit the short-term acute-care DRG model. CMS has focused little on differentiation of patient populations and their disparate clinical needs (other than recognizing that these patients have to stay in acute-care settings for relatively long periods of time).

With implementation of the LTC-DRGs, CMS has begun to explore the value of LTACs, based, in part, on analysis of the relationship among payment, length of stay, and clinical care provided. CMS began the analysis with a 2006 study, attempting to compare markets replete with LTACs to markets without such facilities, focusing on relative costs, cost-effectiveness, and clinical outcomes. The study included recommendations for certification criteria and clinical performance standards for LTACs. The findings suggested that, in aggregate, generally few differences exist in clinical outcomes or cost differences for patients treated in LTAC facilities and those treated in other settings (e.g., a short-term acute-care hospital; rehabilitation unit; skilled nursing facility; or psychiatric hospital). However, the study did demonstrate that for medically complex patients having a higher severity of illness, definite cost savings and improved clinical outcomes were noted for those treated in LTACs. Hence, an important undertaking for clinicians working in LTACs is continued demonstration of the clinical and financial benefits of treating patients in this environment.

Additional challenges for LTACs include a decreasing Medicare payment schedule as patients enroll in managed Medicare and the relative lack of support for LTACs by insurance companies. Many managed care companies do not recognize LTACs as providing a distinct level of care. In fact, their contracts with short-term acute-care hospitals may provide *disincentives* for moving patients to LTACs. Often, insurers have contracts with short-term acute-care hospitals based on a fixed-payment DRG model that, unlike Medicare coverage, does not include "high cost–long stay" payment outliers. In essence, the managed care company pays the acute-care hospital a single payment following patient discharge and does not allow for discharge to another acute-care setting, such as an LTAC. Furthermore, in those health care markets where managed care companies are willing to enter into contracts with LTACs, the insurers define admission requirements very narrowly. The most commonly utilized criteria are derived from InterQual, which delineates evidence-based, clinical decision support standards. In these instances, payment to LTACs is usually on a per diem basis, and each case is classified into one of three or four levels of severity or diagnostic categories.

Finally, LTACs will face a major challenge in the Recovery Auditor program, implemented with passage of CMS legislation and the SCHIP Extension Act of 2007. In late 2008, CMS contracted with Wisconsin Physicians Services (a Medicare administrative contractor) for medical necessity review of patients treated in LTACs. CMS estimated that almost 8% of LTAC admissions were not medically necessary and concluded that it has overpaid providers $215 million annually. The program provides incentives to the Medicare administrative contractor to "guarantee" recovery of at least 75% of the overpayments.

The Future of LTACs: Their Role in the Continuum of Care

Based on the initiative of CMS in sponsoring studies aimed at addressing cost-effectiveness and clinical outcomes (discussed earlier), along with the agency's undertaking of the Recovery Auditors program, CMS and LTACs appear to be gravitating toward a model of delivering medically

complex care. Private insurers also are moving toward this model. Hence, the future role of LTACs will be based on demonstrating their clinical and financial values and on defining their role in the continuum of care.

Models of care built around the successful management of medically complex patients will help the LTAC industry establish itself as a valuable and, perhaps, necessary component of the American health care system. Providers in such an environment are advised to understand and utilize the "all patient refined" DRGs (APR-DRGs), which incorporate severity of illness subclasses into an expanded version of basic DRG categories, as well as InterQual criteria for documenting patient care. Acquisition of such a knowledge base may facilitate optimal positioning of organizations for the inevitable reimbursement challenges that lie ahead.

The LTAC will likely continue to evolve to meet payer requirements in providing a variety of major services, including respiratory care (in particular, ventilator weaning), management of complicated (drug-resistant) infections, and treatment of postsurgical complications and multisystem organ failure. Finally, the LTAC may well serve as a "bridge to rehabilitation," provided the patient has an underlying condition that requires continued acute care and is unable to tolerate the 3 hours of daily physical therapy required for acute inpatient rehabilitation.

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Eskildsen MA: Long-term acute care: a review of the literature. J Am Geriatr Soc 55:775-779, 2007.

This review focuses on the history of, and recent public policy issues related to, growth in LTAC industry.

Jubran A, Grant BJB, Duffner LA, et al: Effect of pressure support vs. unassisted breathing through a tracheostomy collar on weaning duration in patients requiring prolonged mechanical ventilation. A randomized trial. JAMA 309:671-677, 2013.

This randomized controlled trial (RCT) of 316 patients in a single long-term acute care hospital (LTACH) found that patients who required prolonged mechanical ventilation had significantly shorter median weaning times when weaned by unassisted breathing trials using a tracheostomy collar compared to using a pressure support wean (15 days vs. 19 days). However, they found that the two groups had no differences in 6-month mortality (56% vs. 51%) or 12-month mortality (66% vs. 60%).

Kahn JM, Benson NM, Appleby D, et al: Long-term acute care hospital utilization after critical illness. JAMA 303:2253-2259, 2010, doi: 10.1001/jama.2010.761.

This study found that long-term acute-care (LTAC) hospital utilization after critical illness is common and increasing but that survival among Medicare beneficiaries transferred to such facilities after critical illness was poor—approximately 50% 1-year survival after admission to an LTAC hospital.

Kahn JM, Werner RM, David G, et al: Effectiveness of long-term acute care hospitalization in elderly patients with chronic critical illness. Medical Care 51:4-10, 2013.

Survival rates for patients transferred to LTACs and patients remaining in ICUs are similar. Health care costs for those transferred to LTACs are lower, although overall Medicare payments are higher.

Medicare Payment Advisory Commission: Adequacy of Payments for Long-Term Care Hospital Services. Washington, DC: MedPAC, December 2007.

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Medicare Payment Advisory Commission: Report to the Congress: Medicare Payment Policy. Defining Long-Term Care Hospitals. Washington, DC: MedPAC, March 2006, pp 121-135.

Medicare Payment Advisory Commission: Report to the Congress: Medicare Payment Policy. Long-Term Care Hospital Services. Washington, DC: MedPAC, March 2006, pp 207-221.

Medicare Payment Advisory Commission: Report to the Congress: Medicare Payment Policy. Post-Acute Care Providers: An Overview of Issues. Washington, DC: MedPAC, March 2006, pp 153-164.

Each of the above five references addresses, in detail, rules governing Medicare payments to LTACs, as well as proposed changes in policy.

Scheinhorn DJ, Chao DC, Stern-Hassenpflug M, et al: Post-ICU mechanical ventilation: the role of long-term facilities. Chest 120:482-484, 2001.

This review of multiple studies addresses post-ICU weaning success rates and suggests that more than 50% of ventilator-dependent patients can be liberated from mechanical ventilation in long-term care facilities.

Seneff MG, Wagner D, Thompson D, et al: The impact of long-term acute-care facilities on the outcome and cost of care for patients undergoing prolonged mechanical ventilation. Crit Care Med 28:342-350, 2000.

This retrospective analysis compared over 400 ventilator-dependent patients managed in traditional acute care settings with over 1700 ventilator-dependent patients transferred to long-term acute care facilities. While comparable mortality rates were observed, longer mean survival times and lower costs of care were noted for those managed in the long-term setting.

Soisson M: CMS proposed rule: impact on health care. Continuum/ALTHA J Spring:16-19, 2007.

This analysis includes discussion and clarification of the impact on providers of the proposed CMS rule on the requirement for a single episode of care, including both initial acute and LTAC hospital stays.

Unroe M, Kahn JM, Carson SS, et al: One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. Ann Intern Med 153:167-175, 2010.

At one year, survivors of prolonged mechanical ventilation discharged from an ICU setting spent 75% of days in the hospital, in post-acute care facilities, or at home receiving paid home care. The financial burden was substantial.

White AC, O'Connor HH, Kirby K: Prolonged mechanical ventilation: review of care settings and an update on professional reimbursement. Chest 133:539-545, 2008.

The authors provide a description of procedural terminology codes for billing for physician services in managing ventilator-dependent patients in chronic care facilities.

CHAPTER 110

Rapid Response Systems: Rapid Response Teams and Medical Emergency Teams

Scott A. Keeney ■ Babak Sarani ■ William Schweickert

In 2008, the Joint Commission (JC, formerly named the Joint Commission for the Accreditation of Healthcare Organizations, or JCAHO) stipulated that all hospitals in the United States had to implement a system to improve recognition and response to changes in a patient's condition. Its intent was to ensure that all hospital staff members have a suitable method to directly request assistance from specially trained individuals when a patient's condition appeared to be worsening. This represented a significant departure from well-established norms, particularly in teaching hospitals, where the standard of care was for nurses to contact interns initially and information was then passed up the hierarchical chain of command as needed.

In 1999, the Institute of Medicine published *To Err Is Human,* a landmark report which found that a large number of deaths in hospitalized patients were preventable and resulted from negligence, lack of communication, or lack of adequate safety mechanisms. Furthermore, it is now accepted that most cardiac arrests in hospitalized patients are preceded by physiologic changes for hours to days prior to the acute event. The fundamental concept underlying rapid response and medical emergency teams is that timely recognition and intervention by appropriately trained personnel will impact the incidence of cardiac arrest and mortality. In this sense, these teams are meant to serve as the hospital's "911" system to immediately and quickly mobilize resources for patients with acute physiologic deterioration.

Terms and Definitions

One of the goals of the first consensus conference on medical emergency teams was to unify terms used to describe these teams. A rapid response team (RRT) does *not* include a prescribing individual, such as a physician or advanced practitioner. These teams often are led by a nurse and may include a respiratory therapist. An RRT quickly evaluates a patient, initiates basic interventions based on standing orders or protocols, and contacts a physician or advanced practitioner, but cannot initiate advanced therapies. Medical emergency teams (METs) have the capability to prescribe new therapies and are frequently led by a physician from the intensive care unit (ICU) or emergency department. Other team members may include ICU-trained nurses, respiratory therapists, and pharmacists. *Rapid response system (RRS)* describes the overall infrastructure through which RRTs and METs function (Figure 110.1). The RRS includes an afferent arm, which detects signs of impending physiologic deterioration; an efferent arm (RRT or MET) and any needed resources to render treatment; and an administrative arm, which oversees the system and detects trends or recurrent events. The administrative arm collects and analyzes data related to causes of patient deterioration, optimizes methods for the early detection of patient deterioration, and ensures that adequate resources are immediately available to intervene as needed.

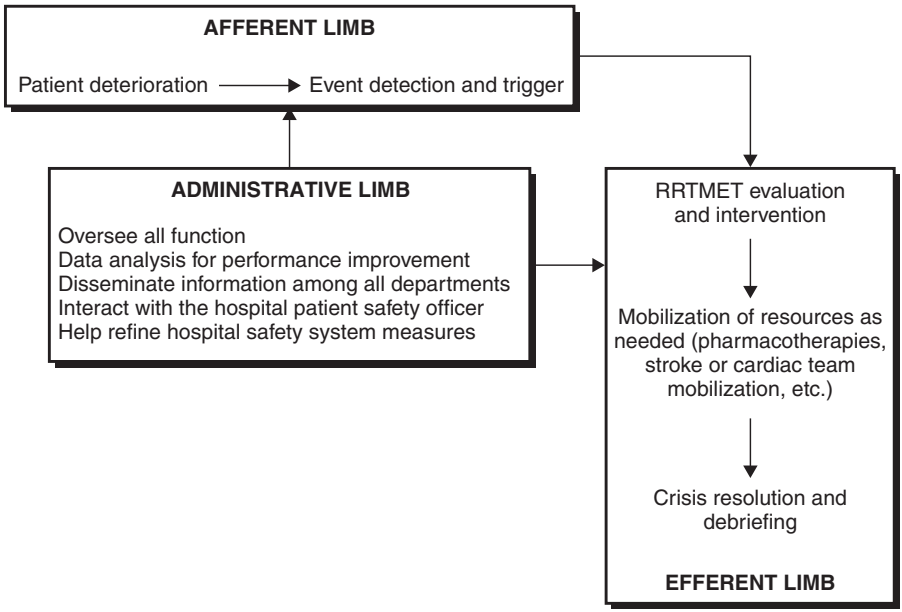


Figure 110.1 Rapid response system design as a performance improvement cycle (see Chapter 109).

Building the Team

Teams can be designed as "ramp up" or "ramp down." Ramp-up teams are usually RRTs and consist of a nurse and/or a respiratory therapist. These personnel are the first to respond to a patient's bedside, assess the patient, and determine what additional resources, if any, are needed. A ramp-up team requires few dedicated resources, and may be most beneficial in places where the call volume and the likelihood for urgent intervention are low. Such places include ambulatory care centers, such as hospital-based clinics and outpatient areas. Ramp-down teams are usually METs and are meant to be an extension of the ICU itself. All personnel respond initially, and those deemed unnecessary are released once the patient has been evaluated. A ramp-down team incurs no delay between the patient assessment and administration of therapy. However, ramp-down teams are very resource intensive and because of their size may foster an air of alarm in the hospital personnel, patient's family, or the patient. These teams may be best suited to areas where the call volume and the need for urgent intervention are high, such as high acuity non-ICU hospital wards.

To optimize the efficacy of the RRS, it is imperative that a review of serious adverse events and cardiac arrest precede team planning. Designed in this way, the RRS can increase patient safety in areas where improvement is needed without impeding well-functioning aspects of the hospital. All hospital staff must then be educated on the role and function of the RRS, a process that usually takes 3 to 6 months. Shortly after implementation, the RRS leadership should solicit feedback from hospital staff and adjust the team to maintain a spirit of cooperation and mutual respect. Obstacles to RRS implementation are discussed later in the chapter.

No optimal criteria for activation of MET/RRT exist. Although many scoring systems have been validated to predict in-hospital mortality or outcomes in the ICU, such as the Acute Physiology and Chronic Health Evaluation (APACHE) and the Simplified Acute Physiology Score (SAPS), none have been validated as triage tools for the bedside assessment of ward patients. The Modified Early Warning Score (MEWS) (Table 110.1) has been validated as a tool to

TABLE 110.1 ■ **Modified Early Warning Score**

Score	3	2	1	0	1	2	3
Respiratory rate (breaths/min)		≤ 8		9–14	15–20	21–29	> 29
Heart rate (beats/min)		≤ 40	41–50	51–100	101–110	111–129	> 129
Systolic blood pressure (mm Hg)	≤ 70	71–80	81–100	101–199		≥ 200	
Urine output (mL/kg/h)	0	< 0.5					
Temperature (° C)		≤ 35.0	35.1–36.0	36.1–38.0	38.1–38.5	≥ 38.6	
Mental status				Alert	Voice	Pain	Unresponsive

From Gardner-Thorpe J, Love N, Wrightson J, et al: The value of Modified Early Warning Score (MEWS) in surgical in-patients: a prospective observational study. Ann R Coll Surg Engl 88:571-575, 2006; and Subbe CP, Kruger M, Rutherford P, Gemmel L: Validation of a modified Early Warning Score in medical admissions. QJM 94:521-526, 2001.

BOX 110.1 ■ Criteria for Activation of the Medical Emergency Team at the Hospital of the University of Pennsylvania

Respiratory

- Respiratory rate < 8/min or > 32/min
- Oxygen saturation < 85% for > 5 min
- Acute increase in supplementary oxygen need > 50%
- Dyspnea

Cardiac

- Heart rate < 40 or > 140 beats per minute
- Systolic blood pressure < 80 or > 200 mm Hg
- Diastolic blood pressure > 110 mm Hg
- New-onset chest pain

Neurologic

- Seizure
- Acute change in mental status

Other

- Uncontrollable bleeding
- Inability to contact housestaff
- Nurse concern/discretion
- Physician concern/discretion
- Family concern

predict the need for ICU admission and mortality in hospitalized patients. Scores of 4 or more are associated with increased mortality and admission to the ICU with a demonstrated sensitivity of 75% and specificity of 83%. Although criteria for activation of the MET/RRT are most often based on physiologic signs, it is imperative to emphasize the importance of medical staff discretion in activating the team (Box 110.1). Since 2009, the JC has stipulated that patients and families also have a means to quickly solicit help from hospital health care providers if the patient or a family member perceives a significant, acute change in the patient's medical condition.

Outcomes Following Implementation of Rapid Response Systems

To date, most reports of the clinical efficacy of the RRS are based on reduction of cardiac arrest rates in single center, retrospective studies. The MERIT trial is the only prospective study evaluating the clinical efficacy of the RRS, utilizing a multicenter, hospital cluster randomization technique to determine if implementation of an RRS would reduce cardiac arrests. Although MERIT identified no significant difference in cardiac arrest rates or mortality between hospitals with and without an RRS, even the authors acknowledged the study was significantly flawed. First, hospitals with an RRS did not utilize it adequately, and only 20% of patients meeting MET criteria were actually evaluated by the team. Second and conversely, hospitals without an RRS utilized their "code teams" to evaluate unstable patients *prior* to cardiac arrest, thereby utilizing them functionally as a MET, thereby "contaminating" the clusters randomized to the non-RRS group. Also, because of the low overall RRS call volume, the study was underpowered to detect a difference. Because of the unpredicted contamination, the investigators grouped all early emergency team calls, defined as calls not associated with cardiac arrest or death, together and reexamined the data in *post hoc* analysis. They found a significant reduction in cardiac arrest rates and unexpected deaths as the number of early emergency team calls increased over the study period. Although this *post hoc* analytic method may overestimate the treatment effect following institution of an RRS, numerous other single center studies similarly found a reduction in cardiac arrest rate, mortality, and need for transfer to the ICU following implementation of an RRS.

Studies on the impact of an RRS beyond cardiac arrest are only beginning to be published. In one study, implementation of a MET significantly decreased the time to antibiotic administration in patients with suspected septic shock. Another study found that time to resuscitation from distributive shock decreased significantly and continuously over 5 years following implementation of a MET. Since mortality improves with early resuscitation of septic shock and timely administration of antibiotics, it is possible that RRS implementation can improve mortality in patients who develop severe sepsis. There have been no studies on other outcomes following RRS implementation, such as treatment of stroke or other emergencies.

Obstacles to Implementation of Rapid Response Systems

Implementation of an RRS can be challenging owing to the cultural change needed for the process to succeed. Physicians must support the possibility that other physicians may consult upon their patients without their explicit approval, such as in a MET model. Nurses must also be comfortable with deviating from traditional models of initially contacting the intern or responsible physician (in nonteaching hospitals) and rather consulting a third party for potentially deteriorating patients. In the RRT system, this may involve a nurse-to-nurse consultation rather than a nurse-physician interaction.

In 2011, there were more than 80,000 annual new nursing graduates in the United States. This presents several challenges. Novice nurses may not appreciate subtle signs of deterioration, thereby preventing prompt RRT activation. In addition, one survey observed that most nurses feel obligated to adhere to the traditional hierarchical physician notification system in a teaching hospital. Another study found that only 10% of nurses would call the MET against the wishes of a physician and that 56% would feel residual tension with the physicians if they did so. Therefore, during the education phase of RRS implementation, nurses must be trained to detect vital signs trends as early warning signs of clinical deterioration, and imbued with confidence that both physician and nurse leaders will support their utilization of the service regardless of physician

consent. Lastly, inexperienced nurses should be encouraged to utilize the nurse-responder on the MET/RRT for consultation if uncertain whether a formal activation of the service is warranted.

Residents generally have two concerns that need to be addressed for successful implementation of the team. First, it should be clear that the RRT/MET does not supplant them. Rather, the RRT/MET should include the resident in all aspects of patient management during and after the acute event. This inclusion particularly applies to housestaff beyond the intern year, addressing their sense of patient "ownership" and ameliorating the tendency to minimize calling for help. One survey found that most medical and surgical residents do not perceive that such inclusive teams detract from their education or learning. Lastly, residents (especially interns) feel that their learning is enhanced if the MET attending provides formal feedback at the completion of the event.

Attending physicians must be convinced that the RRS enhances patient safety and supports their patients when they cannot be present or when patients are potentially deteriorating despite their best efforts. Frequently, physicians do not understand the nursing care limitations that are inherent outside of the ICU. Such limitations may include inability to assess or medicate the patient more frequently than every 2 to 3 hours, or to use certain medications and interventions. Frequently, physicians prescribe appropriate therapy that simply cannot be administered by the non-ICU nurse, and the RRT/MET can be helpful in both educating the medical staff and facilitating a needed ICU transfer.

Aside from the cultural hurdles in implementing the RRS, administrators must support the team both financially and in spirit. This may be difficult as no studies validate many of the end points used during daily operation of the RRS. For example, no prospective studies validate the activation criteria, and some suggest that continuous or more intensive monitoring of patients may be more cost-effective than staffing an RRS. However, given current nursing shortages and the inability to non-invasively and continuously monitor patients without hindering their movement and transportation, how to implement and measure effectiveness of this solution remains uncertain. A benefit of the RRS that can foster administrative support is that an RRS provides a platform to implement solutions across the health system, thereby bypassing the silo effects inherent in departments. Incorporating an effective performance improvement system into the RRS can detect sentinel or recurring events and promote implementing effective solutions across departments, with substantial cost savings and improved outcomes through prevention of medical errors.

Future Research

The MERIT trial failed to demonstrate the efficacy of RRS. Thus, there remains a need to both validate and optimize the efficacy of an RRS. Although the RRT/MET lies at the core of the RRS, additional key components should include quality improvement, feedback, education, and monitoring. Only after these components are clearly validated can an evidence-based approach be established.

Given the many obstacles inherent to validating an RRS, a task force from the International Liaison Committee on Resuscitation standardized definitions and derived standard RRS data elements. The consensus statement distinguished between core and supplemental data elements to aid hospitals in data collection, optimizing system interventions, and improving clinical outcomes. Because the optimal physiologic trigger(s) or timing of activation of a team response are not known, patient information for the 24 hours preceding the point of activation is paramount to the development of an optimal RRS. Supplemental data elements are required for research or to advance the understanding of process-related issues and drive best clinical practice. Universally accepted data elements and definitions will allow aggregate data analysis on an international level. The universal reporting and monitoring of defined core and supplemental elements will ultimately produce a system with evidence-based recommendations and improved clinical outcomes.

Conclusion

Medical errors occur due to one of five failures: to recognize impending deterioration, to intervene, to promptly mobilize resources, to communicate with specialists or other team members, or to prevent future events through implementation of safety systems. An RRS addresses all of these points by implementing detection, effector, and performance improvement arms. Since inception, numerous RRS have emerged to accommodate acute patient needs from small rural hospitals to large academic, tertiary care centers. Clearly, the structure and function of an individual RRS must be tailored to local resources and accommodations, and evidence-based recommendations must emerge.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 111

Telemedicine Applied to the Intensive Care Unit

Craig M. Lilly ■ Steven A. Fuhrman ■ Michael Ries

Telemedicine in the intensive care unit (ICU) allows critical care specialists to increase their reach by eliminating geographic constraints. Advances in telecommunications technology, health information systems, and new modalities for analyzing physiologic parameters derived from bedside monitors represent some of the forces that have led to the ICU-telemedicine movement. In many respects, the rapid growth in the practice of ICU telemedicine parallels that of the patient safety movement (Figure 111.1). Critical care is more frequently being delivered by teams of providers rather than by a single individual. As a result, there often exists a variety of opinions and approaches to patient care. Although much of the care is routine and amenable to standardization, not infrequently what is required involves unplanned, urgent action that necessarily is individualized. This combination of routine and emergent tasks performed by changing teams of episodic providers sets the stage for the application of electronic tools designed to identify the need for care, to standardize the delivery of that care, to enable the use of population management tools, achieve high rates of adherence to ICU best practices, to enable rapid and reliable detection of episodes of physiological instability, observe bedside provider responses, and facilitate interventions when those responses are delayed or ineffective.

Implementing an ICU telemedicine program is one approach to making high-quality routine care available to more critically ill patients while maintaining individualized care for patients who develop unexpected clinical needs By combining health information technology with continuous patient monitoring in an ICU telemedicine program, clinical skill is blended with electronic tools in a care paradigm in which evaluation and management are triggered by patients rather than by providers.

The application of any new technology inevitably results in novel terminology and concepts. Understanding the definitions of these terms is critically important for both the clinical application of telemedicine tools as well as for allowing useful comparisons among ICUs and the proper interpretation of data. Definitions of ICU-telemedicine can be modeled after Medicare's definition of tele-health services as recorded in 42 CFR 410.78, keeping in perspective that Medicare does not recognize telemedicine as a distinct billable service. Using this source, telemedicine is defined as the use of medical information exchanged from one site to another via electronic communications to improve a patient's health. Electronic communication means the use of interactive telecommunications equipment including (but not limited to) audio and video equipment that enables real-time interactive communication between the patient and the clinician at a distant site. Telemedicine is considered an alternative to the traditional way of providing medical care (e.g., face-to-face consultations or examinations between provider and patient). The delivery of ICU telemedicine services when and where they are needed is facilitated by sophisticated notification systems that leverage available patient specific information from laboratory instruments, image interpretation, and physiological monitors. ICU-telemedicine systems vary with regard to the services that they provide and how those services are delivered.

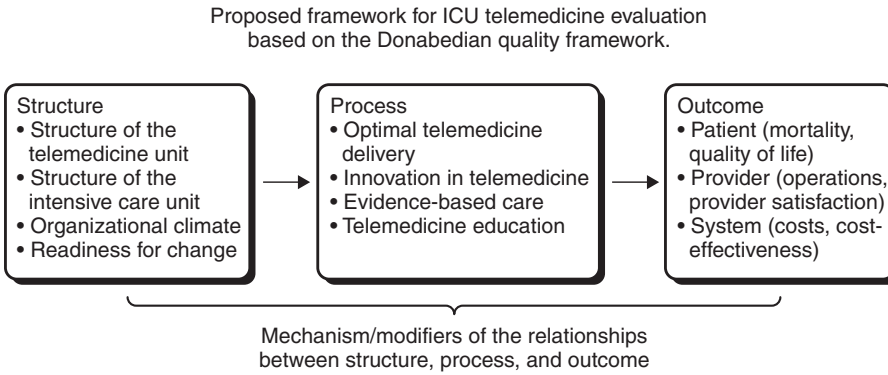


Figure 111.1 Proposed framework for ICU telemedicine evaluation based on the Donabedian quality framework. *(From Kahn JM, Hill NS, Lilly CM, et al: The research agenda in ICU telemedicine: a statement from the Critical Care Societies Collaborative. Chest 140:230-238, 2011. © 2011 by American College of Chest Physicians.)*

Episode-Based or Intermittent Tele-ICU Models

The episodic assessment of an ICU patient can be accomplished using telemedicine tools that are brought to the bedside only when needed. This consultative model that is used by ICU providers is similar to that used to provide tele-stroke services. This type of tele-ICU service is most often triggered by a bedside provider's request for consultation and depends on bedside providers to activate or move the audiovisual equipment to the bedside. Robotic systems require less bedside provider support than systems that bedside providers wheel to the patient because offsite providers can direct them to the patient by remote control. Some systems are able to transmit not only real-time video and audio, but ophthalmoscopic and stethoscopic signals as well. When integrated with hospital information systems, they can also provide patient-specific physiologic, laboratory, radiographic, electrocardiographic, and medical record information, allowing an offsite physician to provide evaluation and management services.

Continuous ICU Telemedicine Services

Systems that deliver continuous ICU telemedicine services incorporate information from the health information system, including signals from physiologic monitors, laboratory instruments, the medical record, and radiographic images. Incorporation of real-time laboratory and physiologic signals from bedside monitors allows the care paradigm to shift from one that is provider initiated to one that is patient triggered, allowing for more urgent evaluation and management. The current generation of systems requires qualified critical care professionals to frequently review alerts and alarms in order to distinguish true clinical deterioration from more frequent false-positive alerts. The majority of alerts emanate from a minority of "unstable" patients. When averaged across the ICU census, patients cared for in a high-acuity academic medical center were found to have about 6.8 true positive alerts for evolving physiologic instability detected in a 24-hour period by an ICU telemedicine service that provides continuous monitoring.

Comprehensive Tele-ICU Services

A comprehensive tele-ICU takes responsibility for providing comprehensive critical care services with the assistance of continuous monitoring technology. These technologies allow the remote provider to detect patient instability or laboratory abnormalities in real time, order diagnostic tests, make diagnoses, implement treatment, arrange procedures or subspecialty consultation,

enable the delivery of evidence-based medicine, manage life-support equipment, actively teach critical care medicine, and communicate with patients, bedside providers, and family members.

Associations of ICU Telemedicine with Outcomes

The justifications given for implementing an ICU telemedicine program often include a desire to increase access to critical care services, to reduce critical care morbidity and mortality, and to provide critical care services more efficiently. ICU telemedicine systems have varied in the way that they have been operationalized, and it is therefore not surprising that the published associations with outcomes have varied. The first reported studies of comprehensive ICU telemedicine implementations were conducted by intensivists who commercialized their system. These studies used an integrated model where tele-ICU providers had full authority and support for modifying care plans. In so doing they demonstrated statistically significant and clinically meaningful associations with lower ICU and hospital mortality and reduced length of stay. Reports from ICU telemedicine programs that used a more restrictive model, allowing bedside physicians to limit the ability of offsite ICU telemedicine providers to modify care plans, have had varied impact on mortality or length of stay. Subsequent reports of ICU telemedicine implementations that have focused on integration of bedside and off-site providers and were conducted by investigators without potential commercial conflicts of interest have reported significant associations with lower mortality, morbidity, cost, and length of stay.

ICU Telemedicine Effects on ICU Processes of Care

Studies that have quantified ICU care delivery processes have consistently shown an association between comprehensive ICU telemedicine and lower mortality and length of stay. These studies have attributed the improvements to such things as adherence with critical care best practices, reducing rates of complications, rapid intensivist review and availability, and responses to alerts and alarms for physiologic instability that are consistently less than 3 minutes. Programs that include an ICU pharmacist on their offsite have reported significant reductions in pharmacy costs as well. Medical centers that have integrated their comprehensive ICU telemedicine programs with their emergency department and postanesthesia care units have used the technology to increase case volume and throughput.

ICU Telemedicine in Community and Rural Hospitals

ICU telemedicine programs that are affiliated with major medical centers allow physicians practicing in community hospitals to care for higher acuity critically ill adults who might otherwise require transfer to a tertiary medical center. Studies have shown that the revenue generated from these cases more than offsets the cost necessary to provide the ICU telemedicine services. For instance, the costs required to manage drug overdose, sepsis, or respiratory failure in a community hospital supported by a comprehensive ICU telemedicine service were strikingly lower than the costs needed to transport and manage similarly matched cases at an academic medical center.

ICU staff members benefit from a comprehensive ICU telemedicine program by having immediate access to critical care specialists who are able to assist in the identification, evaluation, and stabilization of patients with evolving clinical needs. The public benefits from these services because of improved access to trained intensivists being made available over a larger geographic area than would otherwise be possible. Health care systems that utilize telemedicine tools that enable real-time access to critical care professionals in an integrated model of safety and quality management benefit because they can provide high-quality care at lower cost than competitors without an effective ICU telemedicine program.

An annotated bibliography can be found at www.expertconsult.com.

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CHAPTER 112

Transporting the Intensive Care Unit Patient

Alix O. Paget-Brown ■ Robert A. Sinkin

Transporting the trauma patient is a well-established part of medical education. Far different, equally necessary, and of great complexity is transporting the intensive care unit (ICU) patient. Transporting the ICU patient differs from transporting the trauma patient in the absence of an early stabilization phase and in the complex medical decision making and breadth of knowledge of physiology needed to understand and address a multitude of underlying disease conditions.

Reasons for transporting the ICU patient include the need to provide a higher level of care in another hospital, obtain diagnostic testing or procedures within a hospital system, or move a recovering ICU patient to a rehabilitation/chronic care facility.

Initiation of the ICU Transport

The trauma patient needs immediate stabilization and blood loss/fluid and airway management. The ICU patient, in contrast, is usually a study in physiology, requiring sometimes-complex airway and medication management. ICU patients can vary in their level of stability at the time of transport.

The single most important part of the ICU patient transport is the handing off of care between providers. The history provided by the current providers, both physician and nurse or physician extender, is key. Knowing the underlying diagnosis(es) and obtaining a current and accurate list of medications and infusions (including timing and dosing) are essential to care for the patient correctly during transport. Any unusual aspects in managing an individual patient should also be mentioned at this time (e.g., an older adult with a paradoxical agitation response to midazolam as opposed to sedation).

The Airway in Transporting the ICU Patient

Management of the medically ill ICU patient's airway can be especially complex. For those patients already mechanically ventilated, maintenance of the airway provides both advantages and significant challenges.

Certainly, having a stable airway in a mechanically ventilated patient is an advantage. However, whether the patient is ventilated via endotracheal or tracheotomy tube, ensuring that the tube is securely taped or attached and well positioned may be difficult. Transporting a patient inevitably requires several patient movements, on and off of stretchers, and even further shifting the patient several times if the transport is for additional testing. The security of the airway at all times is vital. A chest radiograph obtained immediately prior to transport gives the team confirmation of initial placement. Further confirmation of security/stability and placement should be performed after every movement. This comprises an assessment of the security and depth of the tube, as well as

Additional online-only material indicated by icon.

auscultation to ensure symmetric breath sounds (see Table 112.E1 for appropriate endotracheal tube sizes and depths). Adequate sedation during transport aims to prevent the patient from dislodging the tube or becoming agitated or combative (see Chapter 5). Continuous pulse oximetry should be maintained during transport to aid in assessment of the airway and adequate oxygenation during transport.

Transporting the mechanically ventilated patient requires switching to a transport ventilator, the majority of which are conventional mechanical ventilators. The simplest transport device offers limited modes of support, whereas more complex devices offer a variety of ventilation modes, such as intermittent mandatory ventilation (IMV), assist control, or a combined assist/control mode with pressure or volume control (see Chapter 2). For patients on a conventional mechanical ventilator, a direct switch using the current ventilator settings can often be easily accomplished. However, switching from a more complex mode (e.g., high-frequency ventilation) to a transport ventilator may require a period of stabilization/transition (discussed later). An arterial blood gas (ABG) on the new ventilator at the current settings should be evaluated to address any ventilation needs prior to transport. For prolonged transports to other facilities, ABGs should be checked periodically, ideally every 1 to 2 hours if the patient appears clinically stable and more often if unstable. Ventilator adjustments should be performed gradually, avoiding sudden shifts, but providing the needed support. Any large ventilator changes to combat severe respiratory acidosis and hypercapnia should have blood gases monitored every 30 minutes until stable. Even appropriate blood gases after significant ventilator manipulation must be followed up, as overcorrection and subsequent hyperventilation may occur and be deleterious.

Some patients, more often neonates (discussed later), receive ventilation via high-frequency oscillators or jet ventilators. Some teams have the ability to transport on portable jet ventilators, and in this case, the change should be made directly, again checking the adequacy of ventilation and oxygenation after the switch. If the patient must be transitioned from high-frequency to conventional ventilation for transport, the calculations of approximate mean airway pressures, inspiratory times, inspiratory:expiratory (I:E) ratios, and expected rates should be carefully done prior to the change. This also applies to the switching of patients from a high-frequency oscillator to a jet ventilator for transport.

If the patient is not being mechanically ventilated, concern must be paid to correct positioning of the patient at all times. Sometimes the patient can actively participate in this activity, but in most instances the ICU patient will require continuous efforts by the transport team to ensure adequate oxygenation. The most common modes of oxygen delivery to the nonintubated ICU patient are via nasal cannula or through a nonrebreather mask system, sometimes in conjunction with an oro- or nasopharyngeal airway. Appropriate hand-off of care should include the current oxygen requirement of a nonintubated patient. However, oxygen needs typically increase during transport, and oxygen delivery should be adjusted as needed.

Nonmechanically ventilated patients present a complex picture for transport. Care must be taken to fully evaluate the individual patient's airway, underlying diagnoses, current illness, and any prior diagnoses/conditions that would complicate any endotracheal intubation required during transport, such as morbid obesity or any cervical spine mobility issues. A patient's level of consciousness should be fully assessed prior to the initiation of transport; patients with decreased levels of consciousness or disorientation may not be safe for transport without a stable artificial airway.

Blood Pressure Management in Transporting the ICU Patient

When patients are being picked up for transport at an outside facility by the accepting hospital's team, all infusions are usually redone (recalculated, remixed, and placed on the transport team's equipment) and set to run at the dose given by the primary care team. This process ensures

TABLE 112.E1 ■ **Endotracheal Tube (ETT) Sizes and Depths**

Patient Age (and Weight)	Blade Size	ETT Size	ETT Depth (cm @ the Lips)
< 28 weeks EGA (< 1 kg)	0	2.5 Fr uncuffed	7
28–34 weeks EGA (1–2 kg)	0–1	3.0 Fr uncuffed	8
34–38 weeks EGA (2–3 kg)	1	3.5 Fr uncuffed	9
38+ weeks EGA (> 3 kg)	1	4.0 Fr uncuffed	9–10
1–8 years	1–2	$\frac{\text{Age (years)} + 16}{4}$ uncuffed	Variable
Adult*	2–5	7.5–8.5 Fr cuffed	20–21 in women; 22–23 in men

*Correct depth of tip of ETT for adults is 2.5 to 4.0 cm above main carina.
EGA, estimated gestational age.

consistency with the receiving institution's concentrations and pumps, and it decreases the risk of medication errors by eliminating the need to employ unfamiliar rates or the inability to run certain setups on other pumps. Acute blood pressure shifts are frequent when transiently interrupting pressor infusions. It is essential to individually switch the infusions over to the transport set gradually and allow enough time to resolve hemodynamic changes, establish possibly new baselines, and adjust infusion rates.

As mentioned previously, switching pressor drips can be challenging during the initiation of transport from a referring hospital. During in-hospital transport for procedures, testing, or transfers, however, the currently active infusions can usually be maintained. This avoids many blood pressure swings seen when switching infusions. Most likely the equipment, concentrations, and rates are either identical or compatible, and they are institutionally regulated. Frequently, the patient is returning to the previous nurse and bed location after a procedure or test. When transporting a patient from one's home institution to another facility, ICU team members should take great care to have an adequate supply of medications and infusions for the duration of transport while factoring in possible and unforeseen delays.

Hemodynamic stability may be difficult to maintain on transport, as the stress of transport on the ICU patient may provoke extreme fluctuations in blood pressure. This is especially important to remember when using other commonly used medications on transport, such as sedatives, opioids, and neuromuscular blockers, as sedatives and opioids tend to decrease systemic blood pressure.

Special Cases in ICU Transports

ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome (ARDS) and its milder form, acute lung injury (ALI), are characterized by acute respiratory distress accompanied by pulmonary infiltrates on chest radiograph, the need for positive end-expiratory pressure (PEEP), and varying degrees of hypoxemia. The foremost underlying cause may be sepsis, but other causes include pneumonia, aspiration, and trauma, each requiring different treatment strategies. However, pulmonary physiology management remains similar despite varied etiologies. Current goals remain to optimize lung recruitment, minimize areas of ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch, and minimize subsequent lung damage resulting from ventilator-induced trauma.

Pulmonary management of ARDS on transport remains challenging. Paralysis of the patient is controversial, with 25% to 40% of patients suffering from ARDS receiving some sort of neuromuscular blockade during their hospital course. Although typically for a short duration, paralysis decreases $\dot{V}/\dot{Q}$ mismatch and improves oxygenation and gas exchange, when combined with a high PEEP strategy to avoid dependent atelectasis. A short period of neuromuscular blockade has salutary effects on oxygenation, ventilation, and lung recruitment with a low risk for deleterious side effects. A low-tidal-volume ventilation strategy that enhances survival can usually be continued on transport.

Although pulmonary management may be challenging, the treatment for the underlying etiology of ARDS must be incorporated. This includes antibiotics for the treatment of possible/proven sepsis or pneumonia and hemodynamic support with vasopressor infusions as needed. Close attention to glucose management may prove challenging in this population as corticosteroids may be utilized. Blood sugar should be checked frequently as determined by previous needs and stability per the hand-off of care (discussed earlier in the chapter).



Information about the Neonatal Patient and an annotated bibliography can be found at www.expertconsult.com.

THE NEONATAL PATIENT

The neonatal patient represents a special population in ICU patient transport. With a few exceptions, adults can independently thermoregulate. However, neonates (especially the premature) poorly perform this function due to a high surface area to body weight ratio, a thinner epithelial layer allowing increased fluid losses, poor subcutaneous fat deposition, and an absence of brown fat. The late-preterm infant born between 34 and 37 weeks' gestation, although appearing of sufficient weight, is also at significant risk for hypothermia and poor thermoregulation. For these reasons, neonates and infants require specialized equipment including transport incubators, occasionally used in conjunction with chemical warmers. Chemical warmers are chemically activated gel pads for use under infants. Of note, these chemical warmers are very sensitive to the environmental temperature—the starting temperature of the warmer affects the final temperature achieved by the pad. For example, a cold pad (activated from below room temperature) will not achieve the desired heat level and hypothermia may result. If the pad is activated from an elevated temperature (e.g., after being stored in a hot ambulance during elevated summer temperatures), thermal burns may result from excessive generation of heat. *Therefore, chemical warmers should be stored and activated at room temperature.* Attention should be paid to the infant's temperature throughout transportation, with axillary temperature taken every hour or more frequently if temperature maintenance is an issue. Some incubators monitor continuous rectal temperatures, but care has to be taken to avoid probe displacement.

A special transport situation is the use of therapeutic hypothermia for neuroprotective purposes in cases of hypoxic-ischemic encephalopathy (HIE) (guidelines for qualifying infants are shown in Box 112.E1). Cooling infants, either with whole-body cooling to 33.0° to 34.0° C, monitored with rectal or esophageal temperature probes or via head cooling, improves neurologic outcomes in infants without significant adverse effects such as the development of persistent pulmonary hypertension or the need for extracorporeal membranous oxygenation. If the core temperature cannot be measured continuously during transport, it should be measured at intervals of 15 minutes. Skin temperature is not reliable in these infants.

Therapeutic hypothermia has potential complications when associated with transport. These include the inability to actively and in servo-fashion cool the infant, the associated difficulty in achieving and maintaining a stable temperature, and preventing excessive hypothermia during transport. For this reason, many institutions recommend only passive cooling on transport, by turning off the heat in the incubator. Infants with HIE have even poorer thermoregulatory capacity than their normal peers, and merely turning off the radiant warmer while awaiting of the transport team can result in extreme cooling (< 33.0° to 34.0° C) quite rapidly. Even more dangerous is overheating or hyperthermia, which is associated with neurologic morbidities. Whether iatrogenic or patient driven, excessive warming must be avoided.

Premature infants, especially those 30 weeks estimated gestation at birth, are at risk for developing intraventricular hemorrhages because of their immature germinal matrix. Therefore, one should take great care to avoid sudden jolts or bumps during transport; premature infants should be maintained in a neutral (flat) position. During lifting in and out of the ambulance or air transport vehicle, avoiding a head-down position is important. Gel pads are frequently used for this purpose. A head-of-the-bed up position is also undesirable in premature infants because of poor cerebral blood pressure homeostasis.

All sick infants being transported require close monitoring of fluid status. This can be done via indices of perfusion such as urine output, color, and capillary refill time. Tachycardia also develops with hypovolemia, and hypotension is a late and ominous finding in infants. Volume expansion is administered on an mL/kg/day basis, unlike in adults where the volume of fluid is measured in liters and medications are in ampoules. Maintenance fluid is generally 80 to 120 mL/kg/day based on age, hydration, and nutritional status. Some very premature babies or infants in septic

BOX 112.E1 ■ University of Virginia Hypothermia Protocol Qualifying Criteria

Diagnostic Criteria for systemic cooling:

1) ≥ 36 weeks' gestation at birth as measured by best obstetrical estimates
2) ≥ 2000 g birth weight
3) One qualifier in Part A and two or more characteristics in Part B must be met
4) Initiated within 6 hours from time of birth

A

- pH ≤ 7 in cord blood or within 60 minutes of birth or base deficit ≥ 16 in cord blood or within 60 minutes of birth
- If pH 7.01–7.15 or base deficit 10–15.9, ONE additional part A criterion (below) is needed
- Apgar ≤ 5 at 10 minutes after birth
- Continued need for resuscitation including mask ventilation at 10 minutes after birth
- Prolonged fetal bradycardia (HR < 80 bpm) in absence of congenital heart block for > 15 min in utero
- Early post natal code event requiring CPR with suspected hypoxia/ischemia and subsequent encephalopathy

B

- Seizures (no second criterion needed)
- Altered level of consciousness
  - Lethargy (delayed response to stimuli, decreased spontaneous movements)
  - Obtundation
- Decreased or absent spontaneous activity
- Tonic posturing
- Hypotonia
  - Focal or generalized
  - Flaccidity
- Decreased or absent primitive reflexes
- Autonomic dysfunction
  - Periodic breathing, apnea
  - Bradycardia (resting heart rate < 100 bpm with rare accelerations to 120 bpm)
  - Abnormal papillary responses

Exclusion Criteria: Lethal congenital anomaly; severe, uncontrolled shock; uncontrolled bleeding

shock may require > 150 to 200 mL/kg/d. Fluid requirements depend on the underlying etiology of illness and make up a significant part of the hand-off of care in this population.

Both very premature infants and those born late-preterm are at risk for disruptions in glucose homeostasis. Most suffer from hypoglycemia with poor glucose stores, immature gluconeogenesis, and sometimes inappropriate insulin secretion, especially in infants of diabetic mothers. Glucose levels need to be checked frequently and may need adjustment on transport. Glucose homeostasis is best achieved through appropriate dosing with calculation of the dextrose delivery or glucose infusion rate:

$$\text{Dextrose delivery} = \frac{\text{Dextrose (\%)} \times \text{Infusion rate (mL/h)}}{\text{Weight (kg)} \times 6}$$

The minimal dextrose delivery needed for cerebral glucose delivery is 3 to 4 mg/kg/min, with a good starting point of 4 to 6 mg/kg/min for glucose homeostasis. If this rate is insufficient as measured by blood glucose levels (aiming to achieve a target of 50 to 90 mg/dL), glucose delivery should be increased by 1 to 2 mg/kg/min, either via increased total fluid administration or increased dextrose concentration. Peripheral glucose concentration should not exceed 12.5 mg/dL because

of hyperosmolarity and irritation to the veins. Concentrations of glucose greater than 12.5 mg/dL necessitate central venous line placement.

Hypoglycemic infants can be treated with a 2-mL/kg bolus of 10-mg/dL dextrose. This bolus must be followed by beginning a continuous dextrose infusion, or increasing the dextrose delivery of ongoing infusions, as the bolus will increase insulin release in the infant and may result in a subsequent *drop* in blood glucose, contrary to the therapeutic intent. Close monitoring of the blood glucose, between 30 to 60 minutes after an intervention depending on the degree of glucose abnormality, is important. For long transports (> 2 hours), glucose should be monitored every 2 hours unless patient stability has not been historically in doubt.

Medications and drips must be switched over to the transport infusion pumps prior to the initiation of transport, and medication dosing intervals must be respected. These requirements again underscore the importance of a thorough hand-off of care.

The pulmonary management of infants is quite different than that of adults. The very premature infant, born at < 30 weeks' gestation, is at great risk for respiratory distress syndrome (RDS), a primary insufficiency of surfactant. RDS is quite different in etiology from ARDS, in which a secondary deficiency of functional surfactant has been noted. Premature infants with increased work of breathing after birth are often (if not typically) given endotracheally administered exogenous surfactant. The goal of ventilating these premature infants is to avoid barotrauma, volutrauma, and atelectasis, thereby minimizing long-term damage. For this reason, a short I:E (inspiratory/expiratory) ratio of 0.3 to 0.4 is used, as well as "permissive hypercapnia," where blood gases with mild respiratory acidosis are tolerated. The goal in these cases is a pH of 7.25 to 7.35 and pCO_2 45 to 55 mm Hg. In infants with chronic lung disease associated with prematurity and transported at a later age, a similar pH but with pCO_2 of up to 60 mm Hg is acceptable. A tidal volume of 4 to 6 mL/kg is targeted to accomplish this, and a PEEP of 4 to 6 cm H_2O to provide eight to nine ribs expansion on chest radiograph is appropriate to maximize lung recruitment and minimize volutrauma. Blood gases should be checked after transfer to the transport ventilator and again every 2 hours on transport if the infant is stable, making only gradual changes as needed.

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DePuy AM, Coassolo KM, Som DA, Smulian JC: Neonatal hypoglycemia in term, non-diabetic pregnancies. Am J Obstet Gynecol 200:e45, 2009.

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Forel JM, Roch A, Papazian L: Paralytics in critical care: not always the bad guy. Curr Opin Crit Care 15:59-66, 2009.

This is a review of the use of neuromuscular blocking agents in patients with ARDS, which improves oxygenation and pulmonary inflammation when employed early in the course of the disease.

Gainnier M, Roch A, Forel JM: Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. Crit Care Med 32:113-119, 2004.

This study showed the improvements in oxygenation obtained when neuromuscular blocking agents were used early in the course of ARDS.

Halberg B, Olson l, Edqvist I, Blennow M: Passive induction of hypothermia during transport of asphyxiated infants: a risk of excessive cooling. Acta Pædiatrica 98:942-946, 2009.

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Laptook A, Tyson J, Shankaran S and the National Institute of Child Health and Human Development Neonatal Research, et al: Elevated temperature after hypoxic-ischemic encephalopathy: risk factor for adverse outcomes. Pediatrics 122:491-499, 2008.

This is a landmark study showing the adverse consequences of hyperthermia following hypoxic-ischemic encephalopathy.

Shankaran S, Pappas A, Laptook AR, et al: Outcomes of safety and effectiveness in a multicenter randomized, controlled trial of whole-body hypothermia for neonatal hypoxic-ischemic encephalopathy. Pediatrics 122:e791-e798, 2008.

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Tourneux P, Libert JP, Ghyselen L, et al: Échanges thermiques et thermorégulation chez le nouveau-né. (Eng: "Thermal exchange and thermoregulation in the neonate") Archives de Pédiatrie. In Press, Corrected Proof.

This is a good review of thermoregulation in the neonate.

Tsushima K, King LS, Aggarwal NR, et al: Acute lung injury review. Intern Med 48:621-630, 2009.

This is a thorough review of the ALI/ARDS trial.

Sitzwohl C, Langheinrich A, Schober A, et al: Endobronchial intubation detected by insertion depth of endotracheal tube, bilateral auscultation, or observation of chest movements: randomised trial. BMJ 341:c5943, 2010, doi: 10.1136/bmj.c5943 (published November 9, 2010). www.bmj.com/content/341/bmj.c5943.full. Accessed April 7, 2012.

This study showed that depth of endotracheal tube insertion was the best way to detect right main stem bronchial intubation and showed that depths of the ETTs at 20 cm for women and 22 cm at the lips for men corresponded to having the tip of the ETT located 4 cm above the main carina.

Oxygen-Hemoglobin Dissociation Curves

Paul N. Lanken

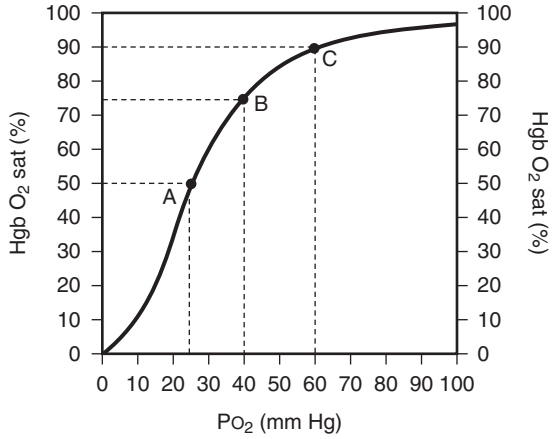


Figure A1 Oxygen-hemoglobin (O_2-Hgb) dissociation curve under normal conditions (pH, Pco_2, and temperature). The oxygen (O_2) saturation of hemoglobin is 50% (abbreviated as P_{50}) at a Po_2 of 26 mm Hg; this P_{50} of 26 mm Hg represents the normal affinity of hemoglobin for oxygen under normal conditions (point A). Under normal conditions, mixed venous blood (i.e., taken from pulmonary artery) and systemic end-capillary blood typically have a Po_2 of ~40 mm Hg with a corresponding O_2 saturation of 75% (point B). The transition from the flat part to the steep part of the O_2-Hgb curve, below which decreases in Po_2 result in clinically relevant falls in O_2 saturation, occurs at Po_2 of ~60 mm Hg with a corresponding O_2 saturation of 90% (point C).

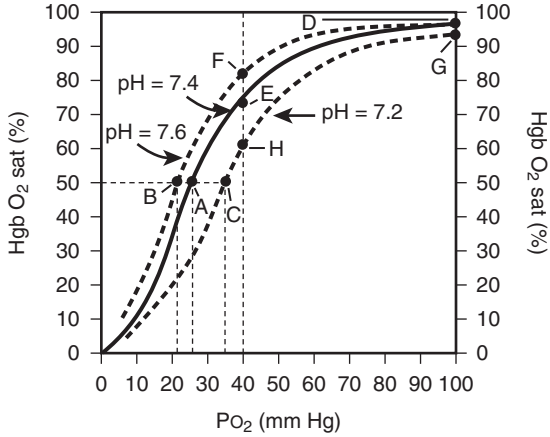


Figure A2 The solid curve is the same O_2-Hgb curve under normal conditions ("normal") as in Figure A1. The dashed curve to the left of the normal curve represents a "shift to the left" of the O_2-Hgb curve due to alkalosis. A similar "shift to the left" would also occur under conditions of decreased temperature or decreased intracellular concentration of organic phosphates (the most important of which is 2,3-diphosphoglycerate [2,3-DPG] in the red blood cells). Decreased concentrations of the latter occur in "banked" red blood cells as they age. A shift to the left also occurs with binding of carbon monoxide to hemoglobin (creating carboxy-hemoglobin or CO-Hgb) or presence of methemoglobin (metHgb) in which the heme-associated iron is oxidized from *ferrous* (Fe^{2+}) to *ferric* (Fe^{3+}). Because the P_{50} has shifted from point A at 26 mm Hg to point B at ~21 mm Hg, a "shift to the left" equates to an *increased affinity* of hemoglobin for oxygen (i.e., increased affinity means that a lower P_{O_2} than normal is needed to saturate 50% of hemoglobin). The dashed curve to the right of the normal curve represents a "shift to the right" of the O_2-Hgb curve due to acidosis. A similar "shift to the right" would also occur with elevated temperature or P_{CO_2}, or *increased* intracellular organic phosphates, especially 2,3-DPG. Increased concentrations of the latter occur physiologically with chronic adaptation to living at a high altitude, chronic hypoxemia, and chronic anemia. Since the P_{50} has shifted from point A at 26 mm Hg to point C at ~35 mm Hg, the "shift to the right" equates to a *decreased affinity* of hemoglobin for oxygen (i.e., it takes a higher P_{O_2} than is normally needed to saturate 50% of the hemoglobin). Note that the O_2 saturations of the three curves are markedly different at P_{O_2} of 40 mm Hg (representing the P_{O_2} of red blood cells at the end of their transit through systemic capillaries). The curve shifted to the left can "unload" *less* oxygen at 40 mm Hg than the normal curve due to its *increased* affinity for oxygen. This unloading is represented by the change in O_2 saturation (vertical height along ordinate) in going from point D to point E on the normal curve compared to going from point D to point F on the curve shifted to the left. In contrast, the curve shifted to the right can "unload" *more* oxygen at 40 mm Hg because of its *decreased* affinity for oxygen. Note the change in O_2 saturation going from point D to point E on the normal curve to going from point G to H on curve shifted to the left. Note that exercising muscles are associated with increased temperature, pH, and P_{aCO_2} in their capillaries—all of which tend to facilitate the unloading of hemoglobin that, in turn, will tend to meet the increased demand of oxygen by the muscle cells. *(See the following for more details: Brewer, GJ: 2,3-DPG and erythrocyte oxygen affinity. Ann Rev Med 25:29-38, 1974, www.annualreviews.org/doi/abs/10.1146/annurev.me.25.020174.000333; accessed January 30, 2012.)*

Tidal Volume Ratios (V_D/V_T)

Paul N. Lanken

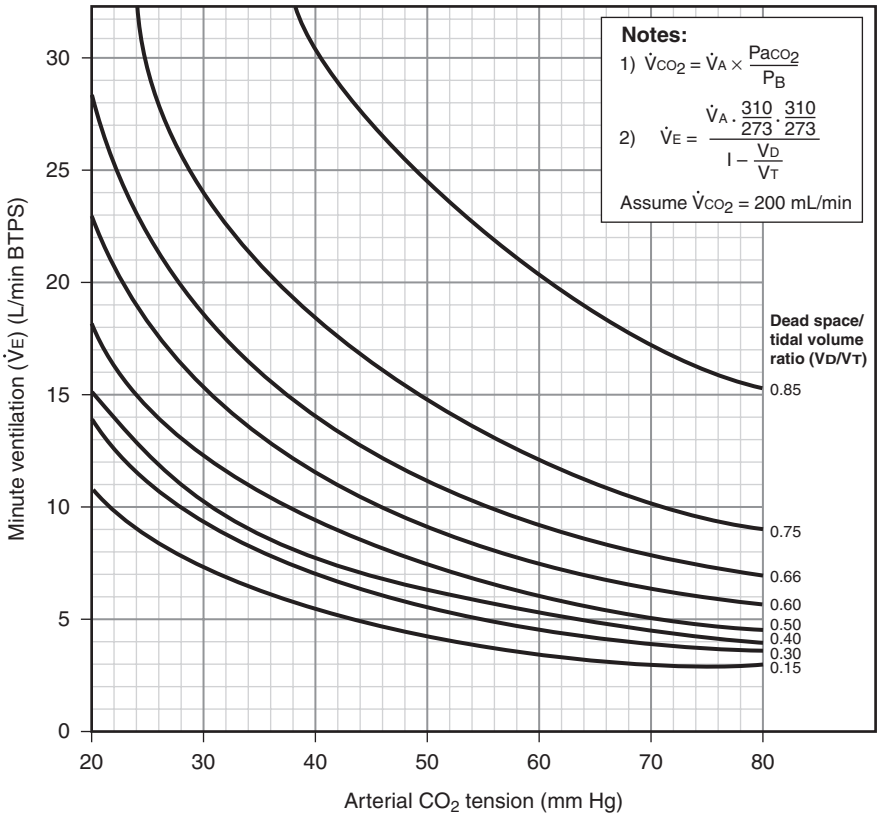


Figure B1 Each curved line is an isopleth with a certain dead space-to-tidal volume ratio [V_D/V_T] (right ordinate). The curves illustrate the relationship between P_{aCO_2} (abscissa) and minute ventilation (left ordinate) for different values of V_D/V_T but at the same $\dot{V}_{CO_2}$ (200 mL/min). (The curves can be derived from Equation 11, Table 1.1, Chapter 1.) One can use this graph to adjust the level of mechanical ventilation for a patient without "overshooting" (i.e., P_{aCO_2} too low) or "undershooting" (i.e., P_{aCO_2} too high). To use, first measure the P_{aCO_2} and the corresponding $\dot{V}_E$ of a ventilated patient. These values will identify which isopleth the patient is "on"—that is, the patient's V_D/V_T. Then follow that curve to the desired P_{aCO_2} and note the $\dot{V}_E$ corresponding to that P_{aCO_2}. Then change the ventilator's respiratory rate (assuming that the patient is not breathing faster than the ventilator's rate) to achieve the new $\dot{V}_E$.

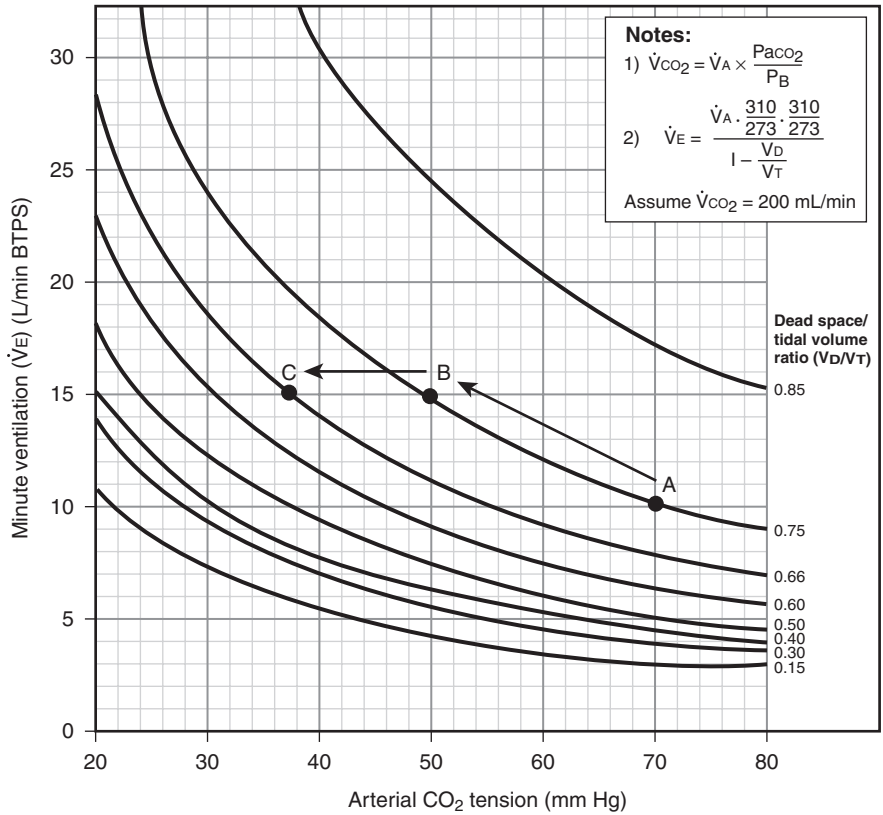


Figure B2 For example, consider a patient with chronic obstructive pulmonary disease (COPD) and chronic CO_2 retention who has a baseline P_{aCO_2} of 50 mm Hg and who has just been intubated and started on mechanical ventilation for acute or chronic respiratory failure. With the ventilation delivering 10 L/min of $\dot{V}_E$ (assuming that the patient's respiratory rate is the set rate on the ventilator), an arterial blood gas indicates that the patient's P_{aCO_2} equals 70 mm Hg. This corresponds to the isopleth with V_D/V_T of 0.75 (point A; such elevated V_D/V_T's are typical of acute flares of COPD). To decrease his P_{aCO_2} to his baseline, 50 mm Hg (but not overshoot which might result in a severe alkalemia), follow the 0.75 isopleth to where it intersects 50 mm Hg (point B) and find that the corresponding $\dot{V}_E$ is 15 L/min. Thus, increasing the ventilator's *rate* to achieve 15 L/min of $\dot{V}_E$ should result in a P_{aCO_2} of ~50 mm Hg. Do not increase the *tidal volume* to increase $\dot{V}_E$, as that would change V_D/V_T (and invalidate the assumption of keeping the V_D/V_T the same). If the patient's V_D/V_T decreases to 0.66 because of increased set tidal volumes, acute treatment for COPD (see Chapter 76), or both, the same $\dot{V}_E$ of 15 L/min will decrease the patient's P_{aCO_2} to slightly below 40 mm Hg and possibly put the patient at risk for a severe alkalemia (point C). Note that one can use Equation 3 in Chapter 2 to arrive at the same result. *(From Selecky PA, Wasserman K, Klein M, Ziment I: A graphic approach to assessing interrelationships among minute ventilation, arterial carbon dioxide tension and the ratio of physiologic dead space to tidal volume in patients on respirators. Am Rev Respir Dis 177:181-184, 1978.)*

Palliative Drug Therapy for Terminal Withdrawal of Mechanical Ventilation

Joshua B. Kayser ■ Tanya J. Uritsky ■ Paul N. Lanken

TABLE C.1 ■ **Stepwise Approach to Palliative Drug Therapy for Terminal Withdrawal of Mechanical Ventilation**

Step 1.	Select agents to be used and route of administration. In general, one should use a **combination** of opioid and benzodiazepine because of their complementary pharmacologic effects: **opioid** to control air hunger and pain and **benzodiazepine** to sedate and to control anxiety. In order to rapidly titrate their doses to the desired effect, the agents, in general, should be given as intravenous (IV) **bolus** injections followed by **continuous** IV infusions.
Step 2.	If the patient is receiving a neuromuscular blocking agent, stop its administration. Allow its effects to wear off or reverse the effects if possible (see Chapter 6) prior to extubation or start of terminal weaning.
Step 3.	Anticipate that *additional* opioid or sedative will be needed for palliation after withdrawal of mechanical ventilation (i.e., preemptive dosing). In this case, at least 30 minutes *before* extubation or start of terminal weaning, give an IV bolus of the agent followed by continuous IV infusion. The IV infusion rate should be a certain fraction of the last bolus dosage given, depending on the agent chosen. (See Tables C.E1 to C.E6.) If no additional opioid or sedative is judged to be needed before withdrawal from assisted ventilation, continue current level of palliative drug therapy and proceed to step 7.
Step 4.	Titrate the dose of agent (steps 5 and 6) to desired effect. Adequacy of palliation can be judged by the appropriate level of sedation (e.g., a Richmond Agitation-Sedation Scale [RASS] of –3 to –5; see Chapter 5) and lack of signs or symptoms of pain, anxiety, fear, dyspnea, tachypnea (e.g., respiratory rate < 25/min), or other discomfort. Whenever additional doses are given, document in the medical record that the dose was given in order to control specific signs and symptoms of distress, that is, it was being titrated to (the appropriate palliative) effect. It is often helpful to the bedside caregivers to be specific in one's medical orders to hold additional boluses if the patient's respirations are less than a certain minimal rate (e.g., 10/min; see step 10).
Step 5.	If desired effect is not achieved within 15 min, repeat IV bolus of drug at *double* the dosage of the prior bolus and increase the rate of the continuous infusion by 25%. See step 10 if this results in a respiratory rate < 10/min.
Step 6.	If desired effect is still *not* achieved, repeat step 5. If using a combination of an opioid and benzodiazepine, alternate between each agent when repeating step 5.
Step 7.	When desired effect *is* achieved, continue the IV infusion at the same rate and extubate the patient or begin the terminal wean.
Step 8.	Reassess level of palliation and responsiveness, using signs listed in step 4, every 15 min (or at shorter or longer intervals as the clinical condition of the patient dictates).

Continued on the following page

TABLE C.1 ■ **Stepwise Approach to Palliative Drug Therapy for Terminal Withdrawal of Mechanical Ventilation—cont'd**

Step 9.	If the patient exhibits discomfort, repeat bolus at double the dosage of the most recent bolus and increase the rate of the continuous infusion by 25%. If discomfort persists, repeat this step until desired effect is again achieved. Administer doses based on the frequency described in step 8.
Step 10.	If the respiratory rate falls below 10/min, continue at the same IV infusion rate but do not give more boluses or increase the IV infusion rate unless the patient is clearly in pain or distress. Anticipate that the family may misinterpret *agonal* respirations as representing patient discomfort and prepare them accordingly (see Chapters 102 and 105 for suggested communication skills). If the patient's blood pressure or pulse falls, do not decrease dose or rate but continue as indicated in steps 4 through 9.

From Marr L, Weissman DE: Withdrawal of ventilator support from the dying adult patient. J Support Oncol 2:283-288, 2004.

See online resources for guidelines for dosing for the following agents: morphine, fentanyl, hydromorphone, lorazepam, midazolam, and diazepam.

TABLE C.E1 ■ **Morphine Sulfate Dosing for Terminal Withdrawal from Mechanical Ventilation**

Exposure to Agent over Prior 24 h*	Bolus Dosing	Continuous Intravenous (IV) Infusion
0–10 mg/h	1. If patient is not at desired level of palliation (see step 4, Table C.1), give 5–10 mg IV "push" at least 30 min before extubation or start of terminal wean. 2. After 15 min, if desired level of palliation has not been achieved, double the prior dosage and give as a repeat bolus. 3. Repeat step 2 as needed until desired end point of symptom control is reached (see steps 4–9, Table C.1). 4. If step 3 is reached, consider using combination therapy with a benzodiazepine as described in Table C.1.	Immediately after the bolus, start a continuous IV infusion at 50% of the bolus dose per hour. Appropriate solutions can be made up by dissolving 150 mg of morphine sulfate in 150 mL normal saline or 5% dextrose solution, yielding a concentration of 1 mg/mL. If the patient requires reboluses, increase the drip by 25% after each bolus (see steps 4–9, Table C.1).
> 10 mg/h	1. If patient is not at desired level of palliation (see step 4, Table C.1), double the maximal hourly dose of morphine administered in the prior 24 h and give it as an IV bolus. 2. After 15 min, if desired level of palliation has not been achieved, double the prior dosage and give as a repeat bolus. 3. Repeat step 2 as needed until desired end point of symptom control is reached (see steps 4–9, Table C.1). 4. If step 3 is reached, consider using combination therapy with a benzodiazepine as described in Table C.1.	Immediately after the bolus, start a continuous IV infusion at 50% of the bolus dose per hour. Appropriate solutions can be made up by dissolving 250 mg of morphine sulfate in 250 mL normal saline or 5% dextrose solution, yielding a concentration of 1 mg/mL. If the patient requires reboluses, increase the drip by 25% after each bolus (see steps 4–9, Table C.1).

*Mean hourly dose over prior 24 hours.

From Truog RD, Campbell ML, Curtis JR, et al: Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American College of Critical Care Medicine. Crit Care Med 36:953-963, 2008; Marr L, Weissman DE: Withdrawal of ventilator support from the dying adult patient. J Support Oncol 2004;2:283-288; Von Gunton C, Weissman DE: Symptom Control for Ventilator Withdrawal in the Dying Patient, 2nd ed. Fast Facts and Concepts. July 2005; 34, available at www.eperc.mcw.edu, accessed February 2012; Kompanje EJO, van der Hoven B, Bakker J: Anticipation of distress after discontinuation of mechanical ventilation in the ICU at the end of life. Intensive Care Med 34:1593-1599, 2008.

TABLE C.E2 ■ **Fentanyl Dosing for Terminal Withdrawal from Mechanical Ventilation**

Exposure to Agent over Prior 24 h*	Bolus Dosing	Continuous Intravenous (IV) Infusion
0–100 μg/h	1. If patient is not at desired level of palliation (see step 4, Table C.1), give 100–200 μg IV "push" (as described in Table C.E1). 2. Refer to steps 4–9 of Table C.1 for continued symptom management.	Immediately after the bolus, start a continuous IV infusion at 50% of the bolus dose per hour. Appropriate solutions can be made up by dissolving 4 mg of fentanyl in 250 mL normal saline or 5% dextrose solution, yielding a concentration of 16 μg/mL. Refer to steps 4–9 of Table C.1 for continued symptom management.
> 100 μg/h	1. If patient is not at desired level of palliation (see step 4, Table C.1), double (2×) the maximal hourly dose of fentanyl administered in the prior 24 h and give it as an IV bolus (as described in Table C.E1). 2. Refer to steps 4–9 of Table C.1 for continued symptom management.	Immediately after the bolus, start a continuous IV infusion at 50% of the bolus dose per hour. Appropriate solutions can be made up by dissolving 4 mg of fentanyl in 250 mL normal saline or 5% dextrose solution, yielding a concentration of 16 μg/mL. If desired, fentanyl can be made up at higher concentrations: 20 μg/mL (5 mg in 250 mL), 50 μg/mL (12.5 mg in 250 mL), 100 μg/mL (25 mg in 250 mL). Refer to steps 4–9 of Table C.1 for continued symptom management.

*Mean hourly dose over prior 24 hours.

From Truog RD, Campbell ML, Curtis JR, et al: Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American College of Critical Care Medicine. Crit Care Med 36:953-963, 2008.

TABLE C.E3 ■ **Hydromorphone Dosing for Terminal Withdrawal from Mechanical Ventilation**

Exposure to Agent over Prior 24 h*	Bolus Dosing	Continuous Intravenous (IV) Infusion
0–2 mg/h	1. If patient is not at desired level of palliation (see step 4, Table C.1), give 1–2 mg IV "push" at least 30 min before extubation or start of terminal wean. 2. After 15 min, if desired level of palliation has not been achieved, double the prior dosage and give as a repeat bolus. 3. Repeat step 2 as needed until desired end point of symptom control is reached (see steps 4–9, Table C.1). 4. If step 3 is reached, consider using combination therapy with a benzodiazepine as described in Table C.1.	Immediately after the bolus, start a continuous IV infusion at 50% of the bolus dose per hour. Appropriate solutions can be made up by dissolving 150 mg hydromorphone in 150 mL normal saline or 5% dextrose solution, yielding a concentration of 1 mg/mL. If the patient requires reboluses, increase the drip by 25% after each bolus (see steps 4–9, Table C.1).
> 2 mg/h	1. If patient is not at desired level of palliation (see step 4, Table C.1), double the maximal hourly dose of hydromorphone administered in the prior 24 h and give it as an IV bolus. 2. After 15 min, if desired level of palliation has not been achieved, double the prior dosage and give as a repeat bolus. 3. Repeat step 2 as needed until desired end point of symptom control is reached (see steps 4–9, Table C.1). 4. If step 3 is reached, consider using combination therapy with a benzodiazepine as described in Table C.1.	Immediately after the bolus, start a continuous IV infusion at 50% of the bolus dose per hour. Appropriate solutions can be made up by dissolving 250 mg of hydromorphone in 250 mL normal saline or 5% dextrose solution, yielding a concentration of 1 mg/mL. If the patient requires reboluses, increase the drip by 25% after each bolus (see steps 4–9, Table C.1).

*Mean hourly dose over prior 24 hours.

From Marr L, Weissman DE: Withdrawal of ventilator support from the dying adult patient. J Support Oncol 2:283-288, 2004; Truog RD, Campbell ML, Curtis JR, et al: Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American College of Critical Care Medicine. Crit Care Med 36:953-963, 2008.

TABLE C.E4 ■ **Lorazepam Dosing for Terminal Withdrawal from Mechanical Ventilation**

Exposure to Agent over Prior 24 h*	Bolus Dosing	Continuous Intravenous (IV) Infusion
0–2 mg/h	1. If patient is not at desired level of palliation (see step 4, Table C.1), give 2–4 mg IV "push" at least 30 min before extubation or start of terminal wean. 2. After 15 min, if desired level of palliation has not been achieved, double the prior dosage and give as a repeat bolus. 3. Repeat step 2 as needed until desired end point of symptom control is reached (see steps 4–9, Table C.1). 4. If step 3 is reached, consider using combination therapy with an opioid as described in Table C.1.	Immediately after the bolus, start a continuous IV infusion at 50% of the bolus dose per hour. Appropriate solutions can be made up by dissolving 100 mg of lorazepam in 250 mL normal saline or 5% dextrose solution, or 200 mg in 500 mL normal saline or 5% dextrose solution, yielding a concentration of 0.4 mg/mL. If the patient requires reboluses, increase the drip by 25% after each bolus (see steps 4–9, Table C.1).
> 2 mg/h	1. If patient is not at desired level of palliation (see step 4, Table C.1), double the maximal hourly dose of lorazepam administered in the past 24 h, and give as an IV bolus. 2. After 15 min, if desired level of palliation has not been achieved, double the prior dosage and give as a repeat bolus. 3. Repeat step 2 as needed until desired end point of symptom control is reached (see steps 4–9, Table C.1). 4. If step 3 is reached, consider using combination therapy with an opioid as described in Table C.1.	Immediately after the bolus, start a continuous IV infusion at 50% of the bolus dose per hour. Appropriate solutions can be made by dissolving 100 mg of lorazepam in 250 mL normal saline or 5% dextrose solution, or 200 mg in 500 mL normal saline or 5% dextrose solution, yielding a concentration of 0.4 mg/mL. If the patient requires reboluses, increase the drip by 25% after each bolus (see steps 4–9, Table C.1).

*Mean hourly dose over prior 24 hours.

From Marr L, Weissman DE: Withdrawal of ventilator support from the dying adult patient. J Support Oncol 2:283-288, 2004; Truog RD, Campbell ML, Curtis JR, et al: Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American College of Critical Care Medicine. Crit Care Med 36:953-963, 2008. Jacobi J, Gilles LF, Coursin DB, et al: Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 30:119-141, 2002.

TABLE C.E5 ■ **Midazolam Dosing for Terminal Withdrawal from Mechanical Ventilation**

Exposure to Agent over Prior 24 h*	Bolus Dosing	Continuous Intravenous (IV) Infusion
0–4 mg/h	1. If patient is not at desired level of palliation (see step 4, Table C.1), give 2–8 mg IV "push" (as described in Table C.E3).† 2. Refer to steps 4–9 of Table C.1 for continued symptom management.	Immediately after the bolus, start a continuous IV infusion at 50% of the bolus dose per hour. Appropriate solutions can be made up by dissolving 100 mg of midazolam in 100 mL normal saline or 5% dextrose solution, yielding a concentration of 1 mg/mL. Refer to steps 4–9 of Table C.1 for continued symptom management.
> 4 mg/h	1. If patient is not at desired level of palliation (see step 4, Table C.1), double the maximal hourly dose of midazolam administered in the past 24 h, and give as an IV bolus. 2. Refer to steps 4–9 of Table C.1 for continued symptom management.	Immediately after the bolus, start a continuous IV infusion at 50% of the bolus dose per hour. Appropriate solutions can be made up by dissolving 100 mg of midazolam in 100 mL normal saline or 5% dextrose solution, yielding a concentration of 1 mg/mL. Refer to steps 4–9 of Table C.1 for continued symptom management.

*Mean hourly dose over prior 24 hours.

†Suggested starting doses 0.1 to 0.3 mg/kg IV bolus dose. But patients who are naïve to benzodiazepines may experience sufficient sedation from a 2-mg dose. For patients with prior exposure to midazolam, bolus doses can be initiated at double that of the 24-hour rate.

From Von Gunton C, Weissman DE: Symptom Control for Ventilator Withdrawal in the Dying Patient, 2nd ed. Fast Facts and Concepts. July 2005; 34, available at www.eperc.mcw.edu, accessed February 2012; Kompanje EJO, van der Hoven B, Bakker J: Anticipation of distress after discontinuation of mechanical ventilation in the ICU at the end of life. Intensive Care Med 34:1593-1599, 2008.

TABLE C.E6 ■ **Diazepam Dosing for Terminal Withdrawal from Mechanical Ventilation**

Exposure to Agent over Prior 24 h*	Bolus Dosing	Continuous Intravenous (IV) Infusion
0–60 mg/h	1. If patient is not at desired level of sedation, give a 10–20 mg IV bolus. 2. After 30 min, if desired level of sedation is still not achieved, then give 20–40 mg as an IV bolus. 3. If desired effect is seen at 30 min postbolus, repeat boluses of same dose q2h. Repeat this step until desired end point is reached. 4. If patient "breaks through" with signs of discomfort prior to 2 h, repeat steps 1 and 2 and give routine boluses every hour.	Diazepam is not recommended for use as a continuous infusion due to the long half-lives of the parent compound and its active metabolite (see Chapter 5) as well as potential for precipitation in IV fluids and absorption of drug into infusion bags and tubing.
> 60 mg	1. If patient is not at desired level of sedation, give the maximal bolus given over the past 8 h as an IV bolus. 2. After 30 min, if desired level of sedation is still not achieved, then double the prior dosage and give as a repeat bolus. 3. If desired effect is reached after 30 min, repeat bolus at same dosage at 2 h intervals. 4. If patient "breaks through" with signs of discomfort prior to 2 h, repeat steps 1 and 2 and repeat routine boluses every hour.	Diazepam is not recommended for use as a continuous infusion due to the long half-lives of the parent compound and its active metabolite (see Chapter 5) as well as potential for precipitation in IV fluids and absorption of drug into infusion bags and tubing.

*Mean hourly dose over prior 24 hours.

From Jacobi J, Gilles LF, Coursin DB, et al: Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 30:119-141, 2002. Roche Pharmaceuticals. Valium® (diazepam) injection prescribing information. Nutley, NJ; 1999.

Advanced Cardiac Life Support (ACLS) Algorithms*

American Heart Association

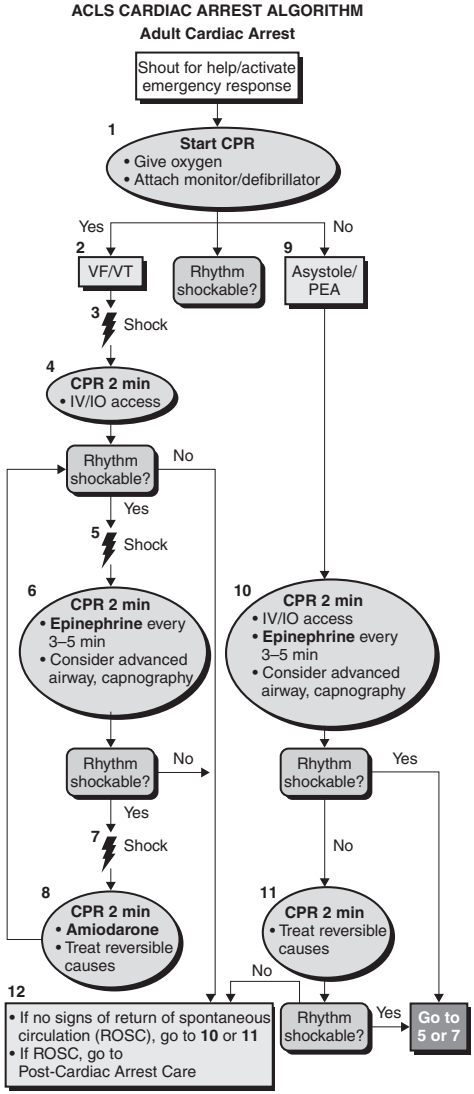


Figure D1 Advanced cardiac life support (ACLS) algorithm for ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT). ABCs, airway, breathing, and circulation; CPR, cardiopulmonary resuscitation; IV, intravenous; IO, intraosseous; J, joules.

*Algorithms in Appendix D are from the American Heart Association: Advanced Cardiac Life Support.
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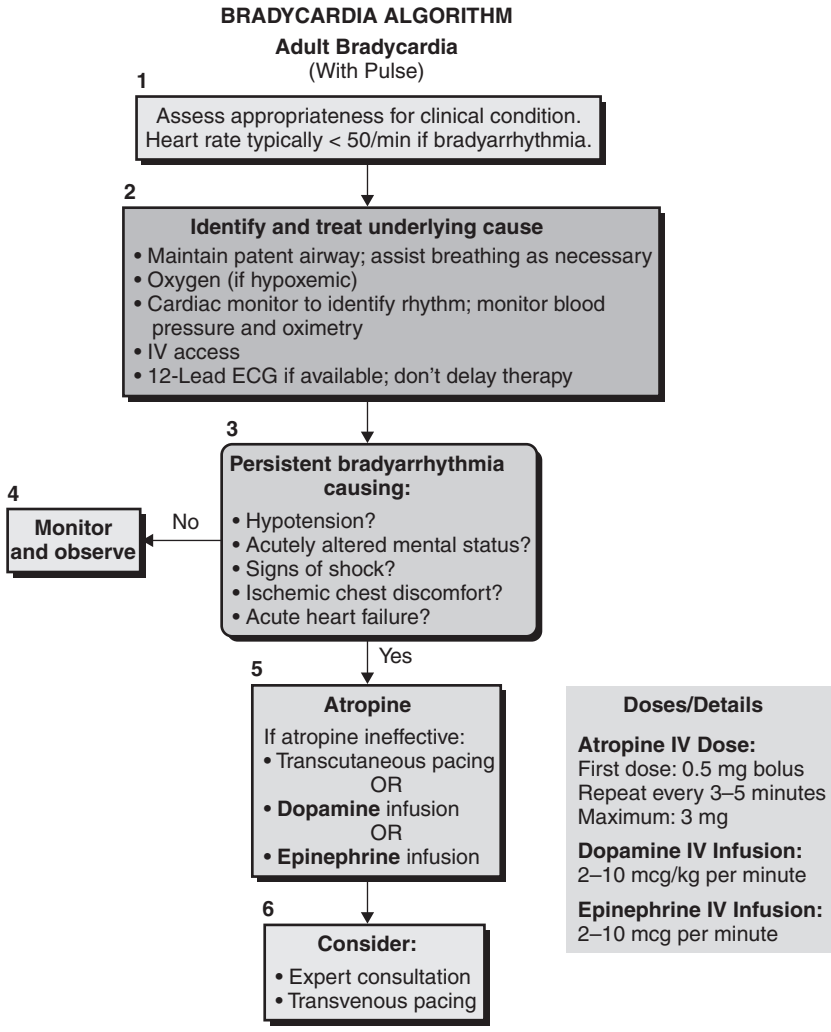
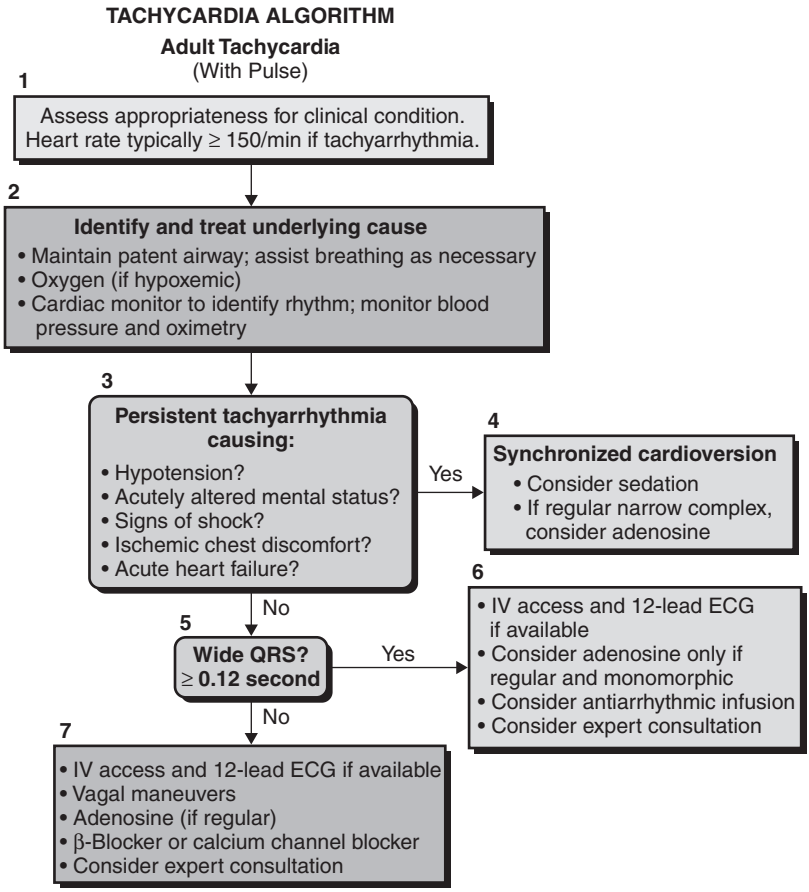


Figure D2 ACLS algorithm for treatment of asystole. CPR, cardiopulmonary resuscitation; ECG, electrocardiogram; IV, intravenous.



Doses/Details

Synchronized Cardioversion
Initial recommended doses:
- Narrow regular: 50–100 J
- Narrow irregular: 120–200 J biphasic or 200 J monophasic
- Wide regular: 100 J
- Wide irregular: defibrillation dose (NOT synchronized)

Adenosine IV Dose:
First dose: 6 mg rapid IV push; follow with NS flush.
Second dose: 12 mg if required.

Antiarrhythmic Infusions for Stable Wide-QRS Tachycardia

Procainamide IV Dose:
20–50 mg/min until arrhythmia suppressed, hypotension ensues, QRS duration increases > 50%, or maximum dose 17 mg/kg given. Maintenance infusion: 1–4 mg/min. Avoid if prolonged QT or CHF.

Amiodarone IV Dose:
First dose: 150 mg over 10 minutes.
Repeat as needed if VT recurs.
Follow by maintenance infusion of 1 mg/min for first 6 hours.

Sotalol IV Dose:
100 mg (1.5 mg/kg) over 5 minutes.
Avoid if prolonged QT.

Figure D3 ACLS algorithm for treatment of tachycardia with pulse. ABCs, airway, breathing, and circulation; BPM, beats per minute; CHF, congestive heart failure; CPR, cardiopulmonary resuscitation; ECG, electrocardiogram; IV, intravenous; J, joules; NS, normal (0.9%) saline; QRS, QRS interval on ECG; QT, QT interval on ECG; VT, ventricular tachycardia.

APPENDIX E

Tables of Height, Predicted Body Weight (PBW), and Tidal Volumes of 4-to-8 mL/kg PBW for Females and Males

Acute Respiratory Distress Syndrome Clinical Trials Network (ARDS Network or ARDSNet), National Institutes of Health (NIH), National Heart, Lung and Blood Institute (NHLBI)

TABLE E1 ■ **Predicted Body Weight (PBW) and Tidal Volume/kg PBW for Females***

Height feet, inches (total in inches)	PBW (kg)	4 mL	5 mL	6 mL	7 mL	8 mL
4′ 0″ (48)	17.9	72	90	107	125	143
4′ 1″ (49)	20.2	81	101	121	141	162
4′ 2″ (50)	22.5	90	113	135	158	180
4′ 3″ (51)	24.8	99	124	149	174	198
4′ 4″ (52)	27.1	108	136	163	190	217
4′ 5″ (53)	29.4	118	147	176	206	235
4′ 6″ (54)	31.7	127	159	190	222	254
4′ 7″ (55)	34	136	170	204	238	272
4′ 8″ (56)	36.3	145	182	218	254	290
4′ 9″ (57)	38.6	154	193	232	270	309
4′ 10″ (58)	40.9	164	205	245	286	327
4′ 11″ (59)	43.2	173	216	259	302	346
5′ 0″ (60)	45.5	182	228	273	319	364
5′ 1″ (61)	47.8	191	239	287	335	382
5′ 2″ (62)	50.1	200	251	301	351	401
5′ 3″ (63)	52.4	210	262	314	367	419
5′ 4″ (64)	54.7	219	274	328	383	438
5′ 5″ (65)	57	228	285	342	399	456
5′ 6″ (66)	59.3	237	297	356	415	474
5′ 7″ (67)	61.6	246	308	370	431	493
5′ 8″ (68)	63.9	256	320	383	447	511
5′ 9″ (69)	66.2	265	331	397	463	530
5′ 10″ (70)	68.5	274	343	411	480	548
5′ 11″ (71)	70.8	283	354	425	496	566
6′ 0″ (72)	73.1	292	366	439	512	585
6′ 1″ (73)	75.4	302	377	452	528	603
6′ 2″ (74)	77.7	311	389	466	544	622

TABLE E1 ■ **Predicted Body Weight (PBW) and Tidal Volume/kg PBW for Females*—Continued**

Height feet, inches (total in inches)	PBW (kg)	4 mL	5 mL	6 mL	7 mL	8 mL
6′ 3″ (75)	80	320	400	480	560	640
6′ 4″ (76)	82.3	329	412	494	576	658
6′ 5″ (77)	84.6	338	423	508	592	677
6′ 6″ (78)	86.9	348	435	521	608	695
6′ 7″ (79)	89.2	357	446	535	624	714
6′ 8″ (80)	91.5	366	458	549	641	732
6′ 9″ (81)	93.8	375	469	563	657	750
6′ 10″ (82)	96.1	384	481	577	673	769
6′ 11″ (83)	98.4	394	492	590	689	787
7′ 0″ (84)	100.7	403	504	604	705	806

TABLE E2 ■ **Predicted Body Weight (PBW) and Tidal Volume/kg PBW for Males***

Height feet, inches (total in inches)	PBW (kg)	4 mL	5 mL	6 mL	7 mL	8 mL
4′ 0″ (48)	22.4	90	112	134	157	179
4′ 1″ (49)	24.7	99	124	148	173	198
4′ 2″ (50)	27	108	135	162	189	216
4′ 3″ (51)	29.3	117	147	176	205	234
4′ 4″ (52)	31.6	126	158	190	221	253
4′ 5″ (53)	33.9	136	170	203	237	271
4′ 6″ (54)	36.2	145	181	217	253	290
4′ 7″ (55)	38.5	154	193	231	270	308
4′ 8″ (56)	40.8	163	204	245	286	326
4′ 9″ (57)	43.1	172	216	259	302	345
4′ 10″ (58)	45.4	182	227	272	318	363
4′ 11″ (59)	47.7	191	239	286	334	382
5′ 0″ (60)	50	200	250	300	350	400
5′ 1″ (61)	52.3	209	262	314	366	418
5′ 2″ (62)	54.6	218	273	328	382	437
5′ 3″ (63)	56.9	228	285	341	398	455
5′ 4″ (64)	59.2	237	296	355	414	474
5′ 5″ (65)	61.5	246	308	369	431	492
5′ 6″ (66)	63.8	255	319	383	447	510
5′ 7″ (67)	66.1	264	331	397	463	529
5′ 8″ (68)	68.4	274	342	410	479	547
5′ 9″ (69)	70.7	283	354	424	495	566
5′ 10″ (70)	73	292	365	438	511	584
5′ 11″ (71)	75.3	301	377	452	527	602
6′ 0″ (72)	77.6	310	388	466	543	621
6′ 1″ (73)	79.9	320	400	479	559	639
6′ 2″ (74)	82.2	329	411	493	575	658
6′ 3″ (75)	84.5	338	423	507	592	676
6′ 4″ (76)	86.8	347	434	521	608	694

Continued on following page

TABLE E2 ■ **Predicted Body Weight (PBW) and Tidal Volume/kg PBW for Males*—Continued**

Height feet, inches (total in inches)	PBW (kg)	4 mL	5 mL	6 mL	7 mL	8 mL
6′ 5″ (77)	89.1	356	446	535	624	713
6′ 6″ (78)	91.4	366	457	548	640	731
6′ 7″ (79)	93.7	375	469	562	656	750
6′ 8″ (80)	96	384	480	576	672	768
6′ 9″ (81)	98.3	393	492	590	688	786
6′ 10″ (82)	100.6	402	503	604	704	805
6′ 11″ (83)	102.9	412	515	617	720	823
7′ 0″ (84)	105.2	421	526	631	736	842

*See Chapter 73, Box 73.3, for details of low tidal volume lung protective ventilatory strategy. © ARDS Network.